EPILEPSY FOUNDATION

SOUTH CENTRAL WISCONSIN

1302 MENDOTA STREET #100
MADISON, WI 53714-1024

Committee on Public Health
January 30, 2008

Testimony on SB 71

Honorable committee members:

My name is Art Taggart, I have been Executive Director with the Epilepsy Foundation South Central Wisconsin for the last 17 years. The Epilepsy Foundation provides direct client services for people and families with epilepsy, as well as public health education programs and advocacy.

The Epilepsy Foundation would like to draw your attention to a disturbing trend in patient care we have experienced over the past several years. Our agency has received an increasing number of calls from consumers who, upon arriving home from the pharmacy, open their pill bottles, and do not recognize the pills they have been dispensed. Some of these patients have brand necessary orders from their physicians but receive generic refills; others are already taking generic medications but their pharmacy has changed suppliers and the pills look different. In several cases, generic formulations from two different manufacturers have been used to fill a single prescription.

We are concerned about patients who have difficult seizure disorders or fragile therapeutic windows suffering unnecessary and expensive therapy failure, not to mention high indirect costs such as loss of driving privilege and lost wages.

SB 71 insures informed consent of the patient and the prescribing physician before a pharmacist dispenses a product different from what has been working for a patient with epilepsy. This will enable physicians to follow and monitor these patients, as well as report adverse incidents to the FDA MedWatch system. Currently, physicians have no mechanism by which to find out when substitute formulations are dispensed, so the MedWatch system has only scant data. Both the American Academy of Neurology and the American Epilepsy Society have charged their members to take the extra time to file these reports.

Consent is only necessary when the product being dispensed is different from what the patient has been taking. Dispense as written rules only serve to indicate that a generic substitution is not permitted. If this is the only method available to physicians to insure continuity of supply, then physicians will have to write more brand name necessary prescriptions, an unintended consequence of current substitution policies and practices.

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www.epilepsyfoundation.org/socentralwisc

SB 71 allows patients with epilepsy to take advantage of lower cost generics safely and with confidence because they and their doctors will be informed any time a different formulation is being dispensed.

SB 71 keeps prescribers informed

Currently, the prescriber only has the authority to order name brand drugs. A physician has no control over which manufactured version of a generic is dispensed from one month to the next. There are 17 different generic manufacturers of one particular epilepsy medication, zonisamide. Physicians have absolutely no comparative information about these products. If a physician attempts to use generics he has no guarantee that his patient will have a continuous supply of the medication that is maintaining control and no method to follow and report incidents caused by formulation differences.

SB 71 removes barriers to access to generic drugs

Patients who have experienced problems when they have been on generic drugs are motivated to spend money out of pocket for more expensive brand name drugs. The FDA and the AMA support generic substitution and the Epilepsy Foundation supports the use of lower cost generic drugs. We believe that SB 71 establishes a best practice of patient education and pharmacist-physician partnership that will help epilepsy patients take full advantage of lower cost alternatives safely and with confidence.

Furthermore, pharmacies will not have to wait until their patients are standing at the counter to obtain consent. When they know they will be changing suppliers they can begin this process at their leisure for prescriptions that they have on file. Some have complained that there are many off label uses for these medications. Consent is only required for those being treated for epilepsy. A pharmacist needs to know the diagnosis anyway, because the information dispensed at the point of sale is different if a medication is being used for the control of seizures as opposed to migraine or other indications.

Mandates

This bill is being called a mandate in the pejorative sense, but people with epilepsy are familiar with mandates. When they experience lost or altered consciousness or involuntary muscle movement they are mandated to surrender their driving privilege for 90 days. It's costly, it's inconvenient, and it doesn't matter why it happened. There are no exceptions. It's a mandate that is intended to insure public safety. SB 71 insures the safety of patients with epilepsy who require unique and individual medication levels to control their seizures.

The FDA and the AMA

The FDA rates a generic as bioequivalent when the absorption rate and bioavailability is between 80 to 125% of the innovator drug with 90% assurance. Bioequivalence is tested on healthy volunteers under very controlled circumstances. People with difficult seizure disorders spend a great deal of energy and effort eliminating variables that might cause breakthrough seizures. The

avoid alcohol, they take their medications at the same times every day and even with the same foods so their bodies absorb the medicine the same way every day. There is such a wealth of anecdotal evidence that small formulation changes add to problems that the FDA has recently agreed to accept experiential data from physicians treating people with epilepsy.

The AMA's Council on Science and Public Health concluded that when a prescription for a generic product is refilled, changing the manufacturer should be discouraged whenever possible to avoid confusion for the patient. They go on to stipulate that for many drugs, especially those with narrow therapeutic indices, drug concentration or pharmacodynamic monitoring is necessary to assure the desired clinical response. This monitoring can be costly and time consuming but is increasingly necessary because of product interchanges. They go on to conclude that patients must receive adequate education to be able to fully understand the nature and proper use of their medications. SB 71 establishes a best practice for patients with epilepsy consistent with each of these important conclusions.

Veterans groups support SB 71

Veteran's organizations have fully supported SB 71. Over 50% of the returning injured Iraqi war veterans have traumatic brain injuries. These veterans are at increased risk of post-traumatic epilepsy as a result of their service injuries. Recently the United States Senate passed a measure that will establish six regional centers of excellence in epilepsy to serve returning vets and we are very hopeful that these centers will be fully funded and that Middleton VA Hospital in Madison will be chosen as one of the sites.

Many of these returning veterans will rehabilitate, go back to work, and participate in the same health plans as you and I. SB 71 insures that they have continuous access to the medications that work for them, or sufficient information to maintain their seizure control despite the vagaries of the marketplace or health policy that puts profits ahead of patients.

Thank you for giving a hearing to this important bill.

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Jim Doyle
Governor

Celia M. Jackson
Secretary

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Committee on Public Health
Representative J.A. Hines, Chairperson

Statement of Greg Weber, R.Ph., Wisconsin Pharmacy Examining Board
2007 Senate Bill 71: Relating to Substitutions by Pharmacists Dispensing Epilepsy Drugs

Room 328, Northwest, State Capitol, Wednesday, January 30, 2008, 9:00 A.M.

Chairperson Hines and members of the Committee, my name is Greg Weber. I serve as vice chair of the Wisconsin Pharmacy Examining Board. Thank you for the opportunity to appear on behalf of the Board. The Board is opposed to 2007 Senate Bill 71. As noted by the Legislative Reference Bureau, under current Wisconsin law a pharmacist may not substitute a drug product equivalent if a prescription indicates that no such substitution may be made (by the prescribing practitioner).

In a January 11, 2008 letter to the Iowa Pharmacy Association, Gary Buehler, R.Ph., Director of the Food and Drug Administration's Office of Generic Drugs made the following statements:

> "FDA is aware that certain individuals and groups have expressed particular concern about the switching of anti-epileptic drug products. To date, we have no scientific evidence that demonstrates a particular problem with this group of products. Further, there are frequently circumstances other than the switch that may cause untoward responses. We continue to follow-up such reports and interact with those concerned."
>
> "If FDA has determined a generic to be therapeutically equivalent to the innovator product, FDA continues to believe that it is not necessary for the healthcare provider to approach any one therapeutic class of drug products differently from any other class when there has been a determination of therapeutic equivalence by FDA for the drug products under consideration."

In summary, the Wisconsin Pharmacy Examining Board opposes 2007 Senate Bill 71 for the following reasons:

1. Current Wisconsin law requires pharmacists to dispense a therapeutically equivalent generic prescription drug if it is lower in cost (Wis. Stats. 450.13(1)).
2. Current Wisconsin law allows prescribing practitioners to prohibit pharmacists from substituting drug product equivalents (generics) (Wis. Stats, 450.13(2)).
3. To date, the FDA has no scientific evidence that there are problems with anti-epileptic drug products and their therapeutic equivalents.
4. If enacted, this legislation will result in higher health care costs for patients, employers, insurers, state and federal government.

Thank you for the opportunity to appear today.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

January 11, 2008

Ms. Nicole Schultz
Iowa Pharmacy Association
8515 Douglas Avenue, Suite 16
Des Moines, IA 50322

Dear Ms. Schultz:

This is in reply to your correspondence dated November 6, 2007, directed to Ms. Susan Winckler requesting that the FDA provide a statement regarding generic substitution, particularly with respect to anti-epilepsy drugs. It was forwarded to the Office of Generic Drugs for a reply.

The FDA has many years of experience in the review of generic drugs and assures the quality and equivalence of approved generic drug products. FDA works with pharmaceutical companies to assure that all drugs marketed in the U.S., both brand-name and generic, meet specifications for identity, strength, quality, purity and potency. In approving a generic drug product, the FDA requires that the proposed generic product is demonstrated to be equivalent to the brand-name drug in both the rate and extent of absorption. As noted in the Preface to the *Approved Drug Products with Therapeutic Equivalence Evaluations* ("Orange Book") (27th Edition),

> FDA classifies as therapeutically equivalent those products that meet the following criteria: (1) they are approved as safe and effective; (2) they are pharmaceutical equivalents in that they (a) contain identical amounts of the same active drug ingredient in the same dosage form and route of administration, and, (b) meet compendial or other applicable standards of strength, quality, purity, and identity; (3) they are bioequivalent; (4) they are adequately labeled; (5) they are manufactured in compliance with Current Good Manufacturing Practice regulations.
>
> FDA considers drug products to be therapeutically equivalent if they meet the criteria outlined above, even though they may differ in certain other characteristics such as shape, scoring configuration, release mechanisms, packaging, excipients (including colors, flavors, preservatives), expiration date/time and other minor aspects of labeling (e.g., the presence of specific pharmacokinetic information) and storage conditions. When such differences are important in the care of a particular patient, it may be appropriate for the prescribing physician to require that a particular brand be dispensed as a medical necessity. With this limitation, however, FDA believes that products classified as therapeutically equivalent will produce the same clinical effect and safety profile as the prescribed product.

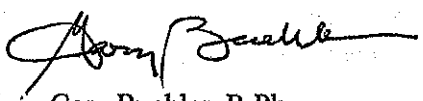
FDA is aware that certain individuals and groups have expressed particular concern about the switching of anti-epileptic drug products. To date, we have no scientific evidence that demonstrates a particular problem with this group of products. Further, there are frequently circumstances other than the switch that may cause untoward responses. We continue to follow-up such reports and interact with those concerned.

If FDA has determined a generic to be therapeutically equivalent to the innovator product, FDA continues to believe that:

- Additional clinical tests or examinations by the healthcare provider are not needed when a generic drug product is substituted for the brand-name product or vice-versa.
- Special precautions are not needed when a formulation or manufacturing change occurs for a drug product provided the change is approved according to applicable laws and regulations by the FDA.
- As noted in the "Orange Book," in the judgment of the FDA, products evaluated as therapeutically equivalent can be expected to have equivalent clinical effects whether the products are brand-name or generic.
- It is not necessary for the healthcare provider to approach any one therapeutic class of drug products differently from any other class when there has been a determination of therapeutic equivalence by FDA for the drug products under consideration.

We continue to monitor, take seriously, and, if indicated, investigate reports of potential inequivalence of all generic drugs. The FDA is committed to approving high-quality generic drug products that can be used with confidence by the American public.

Sincerely,



Gary Buehler, R.Ph.
Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration

cc: S. Winckler
C. Jung

Makers Help Patient Groups Lobby; More Attention to States

By Sarah Rubenstein
July 13, 2007
The Wall Street Journal A1

In state legislatures across the country, the Epilepsy Foundation has been campaigning for bills that would make it harder for pharmacists to switch patients to inexpensive generic epilepsy pills. The effort is getting behind-the-scenes support from drug companies -- a sign of how the industry, long a potent lobbying force in Washington, is increasingly looking to states to achieve its goals.

The foundation, a nonprofit group supported by the drug industry, says switching to generics could cause dangerous seizures. The Food and Drug Administration says it hasn't seen persuasive evidence for that, and it believes each generic is equivalent to the brand-name drug it copies.

Four major brand-name drugs used for epilepsy are expected to lose patent protection and face generic competition between next year and 2010. Those four drugs generated $5 billion in U.S. sales last year, according to IMS Health, meaning the state legislation could have a significant bottom-line impact. Some of the $5 billion figure reflects sales of the drugs for other ailments.

Generic drugs are the centerpiece of efforts to tame growth in America's prescription-drug bill, which topped $270 billion in 2006. When a doctor writes a prescription for a brand-name drug, pharmacists are usually permitted in most states to make an automatic switch to a generic judged equivalent by the FDA.

The epilepsy legislation would carve out an exception to that rule, with many of the bills requiring that doctors explicitly approve such a switch. Tennessee has passed a weaker version that requires doctor notification but not consent. Around 25 other states have considered some form of restriction in the past year.

It isn't the only health issue where states have been the central battleground. Earlier this year, Merck & Co. drew fire for lobbying states to require that preteen girls receive its cervical-cancer vaccine to attend school. Merck stopped its direct lobbying in February, but a group of female state legislators who receive funding from the drug maker continue to push for the laws.

States often move faster than Congress, says Jan Faiks, who runs state policy for the Pharmaceutical Research and Manufacturers of America, or PhRMA, the drug industry's trade group. State legislation can move "from idea, to passage, to governor's signature in 90 days, sometimes faster than that," she says. "So the action is in the states."

Campaign contributions to state candidates by pharmaceutical manufacturers and their employees rose to about $8.8 million for 2006 from about $4.6 million for 2000, according to the National Institute on Money in State Politics. Drug makers spent more than $44 million on state lobbying in 2003 and 2004, the last years for which figures are available, according to the Center for Public Integrity.

In state legislatures, as in Congress, the drug industry often enlists nonprofit health and patient-advocacy groups to advance its agenda. In the epilepsy case, the Epilepsy Foundation's state affiliates, rather than the companies, are taking the most prominent part in the lobbying.

The foundation and its state affiliates receive funding from the epilepsy-drug makers. GlaxoSmithKline PLC and UCB SA donated $500,000 to $999,999 each in fiscal 2006 to the national foundation, according to its annual report. Abbott Laboratories and a Johnson & Johnson unit each contributed $100,000 to $499,999. Representatives of four drug companies sit on the foundation's board, as does PhRMA chief Billy Tauzin.

The foundation and its affiliates had about $77 million in revenue in 2005, about $48 million of which came from state and federal grants.

The foundation says its diverse funding base shields it from undue drug-company influence, and the industry executives on its board didn't

participate in discussions of the drug-switching issue. Foundation leaders note that the state bills would generally require doctor permission for several kinds of switches, including when a patient goes from a generic to a brand.

"These are people's lives that we're talking about -- nothing about stock options and stock value and how this would affect [companies'] bottom line. That would be insulting to us to have discussions like that," says Sindi Rosales, the head of a foundation affiliate in Texas, one of the states that weighed legislation this year. She says pharmaceutical companies are "fabulous partners" and their help in several areas "has been amazingly tremendous," but the companies leave it to the foundation to call the shots.

For their part, company executives describe their lobbying role as limited and say the bills were primarily an initiative of the foundation, although they acknowledge in certain cases that company officials have gotten directly involved. Executives say the aim of these activities is to protect the health of patients. "Our issue is not selfish toward our individual product," says Richard Denness, a vice president at Belgium-based UCB. "It's a real concern in the minds of prescribers. . . . All it takes in the scheme of things are one or two patients to have a tragic event."

In the late 1990s, the national Epilepsy Foundation, based in Landover, Md., raised concerns about anecdotal reports that some patients experienced seizures and side effects after switching epilepsy drugs. Some of the episodes involved patients who had been switched to a generic from a branded drug. The foundation also worried about cases in which patients were switched from one generic version of a drug to another generic version of the same drug.

When the FDA approves generics, it requires manufacturers to show in human studies that their copycat pills deliver a similar amount of active ingredient to the bloodstream as the brand-name original. However, the agency doesn't require exact equivalence. That would be an impossible bar to clear, because there is always a slight variation in the way people absorb drugs.

The foundation theorized that some generic pills had a meaningful difference from the brands. This difference, it postulated, meant patients were getting more or less of the drug in their blood, causing some of them to have seizures or side effects. Foundation officials floated the idea in a 1999 meeting with the FDA.

The FDA's response: "Show us the data," recalls Sandy Finucane, who oversees state and federal policy for the foundation. The agency, unpersuaded by what it saw, stood firm in its long-held position that the difference was too small to have a tangible impact on patients.

Coming up with the kind of evidence the FDA sought would have required a major clinical trial to demonstrate that the seizures were a direct result of the switches, Ms. Finucane says. The foundation thought it would be difficult to enroll patients for such a trial, and the costs were prohibitive, she says. For years the foundation didn't push the matter, beyond developing policy statements and encouraging patients and doctors to report problems to the FDA.

In early 2006, the issue re-emerged as legislation requiring doctor permission for switches was proposed in Illinois. That's the home state of Abbott Laboratories, which makes Depakote, a leading epilepsy pill that is expected to face generic competition next year. The bill passed, but in watered-down form. An Epilepsy Foundation official in Illinois says Abbott helped fund lobbying for stronger provisions that were considered this year but didn't pass. Abbott said it supports some foundation initiatives but declined to give specifics.

In May 2006, the national Epilepsy Foundation convened a committee of medical experts to examine the question. The committee found a lack of authoritative studies showing that such drug switches cause problems, says its chairman, Steven Schachter, a Harvard Medical School neurologist. Nonetheless, it recommended that doctors give explicit approval for switches, citing anecdotal reports of seizures and noting that such attacks can be serious.

Last fall, the American Academy of Neurology issued a statement making a similar recommendation. The academy says it receives funding from drug makers for educational programs but not for developing medical

guidelines.

At a meeting last September, the national foundation told its local affiliates that if they wanted to push for legislation regulating switches, the foundation would provide model legislation and support, Ms. Finucane says. It also told them to "maintain independence from any company that's going to be interested in this issue," she adds. The 50-plus affiliates operate largely autonomously.

The sponsor of a bill in Georgia, state Rep. Charlice Byrd, says a UCB official was the first person to raise the epilepsy-drug switching issue with her. The Belgian company makes the epilepsy drug Keppra. Ms. Byrd says she was sympathetic because her late mother had epilepsy.

Charlotte Thompson, who joined the foundation's Georgia affiliate as executive director last September, says she became aware of the bill after hearing about it from UCB. "When we realized [Rep. Byrd] was introducing this and looked at it and studied what it was, then we jumped on the bandwagon," Ms. Thompson says. Six lobbyists for three companies joined a committee created by the Epilepsy Foundation to work on the legislative process, she says.

Ms. Byrd says several pharmaceutical-company lobbyists offered their support. Abbott lobbyist Guy Mosier "was extremely helpful working with legislators to help them understand the importance and that this piece of legislation was strictly for patient protection," Ms. Byrd says. Mr. Mosier declined to comment.

Ms. Byrd introduced the bill in the Georgia House in January of this year. At a Feb. 7 hearing of the House's health committee, Lasa Joiner, executive director of the Georgia Psychiatric Physicians Association, testified in support. Ms. Joiner was at the time also a Glaxo lobbyist, which she didn't mention at the hearing. In an interview, she said she didn't raise her tie to Glaxo because the company hadn't asked her to lobby for the bill.

Two days later, epilepsy patients and parents of patients visited lawmakers' offices to ask them to support the bill. The Epilepsy Foundation's Ms. Thompson says drug-company lobbyists accompanied the visitors.

Kimberly Oviedo says her 6-year-old daughter had seizures last year after being switched to a generic version of the epilepsy drug Zonegran. She says she supported the bill because she wouldn't "want any other person to have to go through what we've been through with our kids." Ms. Oviedo also has a son who suffers from epilepsy.

The bill passed the Georgia House in a 161-0 vote on Feb. 28, but it stalled in the Senate after groups representing pharmacists and generic-drug makers mounted heftier opposition to it in that chamber. Pharmacies often earn bigger profit margins on generics than on branded drugs.

Ms. Thompson says the foundation plans to meet with the Georgia Senate leadership this summer to try to gather its support for next year.

In Texas, two local Epilepsy Foundation affiliates decided to approach an Abbott official after they resolved to push for a bill, says Ms. Rosales, the head of one of the affiliates. Abbott and other drug makers helped fund the foundation's Texas lobbying, she says.

Ms. Rosales, whose daughter used to have seizures, says she felt deeply about the bill but worried about being perceived as a "mouthpiece for the pharmaceutical industry." She nonetheless hired Santos Alliances, a firm that also represents PhRMA, as her affiliate's lobbyist. Ms. Rosales says it's difficult to find a health-care lobbyist with no drug-maker clients. Frank Santos, head of the lobbying firm, says PhRMA was "absolutely 100% not involved" with the bill.

At a March hearing in the Texas Senate, Ron Hartmann, a lobbyist for a generic-drug maker owned by Novartis AG of Switzerland, testified against the bill. He said he suspected the bill was "less focused on the citizens of Texas than on protecting the market share of a few brand-name drugs that are scheduled to go off-patent in the next few years."

State Sen. Kyle Janek, the bill's sponsor, responded that Mr. Hartmann had "impugned my motivations," and added that, if Mr. Hartmann would "abstain from doing that," then he would abstain from calling Mr. Hartmann a "high-priced shill." Mr. Hartmann apologized. In 2006, Sen. Janek received about $19,000 in campaign contributions from drug makers. He says he sponsored the bill because it was in the best

interests of patients.

The bill passed the state Senate in April, but failed to come up to a vote in the House after debate in that chamber's health committee. Three of the committee's members said in interviews later that they were skeptical of the bill because they thought it was being pushed by drug companies. Generic-drug makers and pharmacists lobbied heavily against the bill.

Meanwhile, some doctors are pushing harder for a study that would settle the matter. Michel Berg, a neurologist who is chairman of an American Epilepsy Society task force examining the switching issue, has opened discussions with the FDA about what kind of trial would be necessary.

For now, Gary Buehler, the director of the FDA's office of generic drugs, says the agency is skeptical that the drug switches cause seizures. "The only way you can somehow pin this down is to do a good study," says Mr. Buehler.

State Senator
Jon Erpenbach

Testimony on Senate Bill 71

Chairman Hines and Members of the Committee, I apologize that I cannot be there in person to testify on this important bill. I would like to submit this written testimony in support of SB 71. It is very important to those with epilepsy that we pass this legislation.

Senate Bill 71 is a patient safety bill that ensures that before a pharmacist substitutes any drug product for treating epilepsy the pharmacist must obtain the consent of the prescribing doctor and the patient. If the pharmacist is dispensing a refill he must also obtain consent from the patient and the treating physician before substituting a different drug than the one previously dispensed.

There are several reasons why this is an important piece of legislation, and a very timely one as well.

- It is estimated by Walter Reed Army Medical Center that 61% of returning service men and women have sustained traumatic brain injuries as a result of daily attacks by rocket-propelled grenades, mines, and improvised explosive devices in Iraq and Afghanistan. These brain injuries are the leading cause of epilepsy and it could mean an increase in epilepsy medication dispensed in Wisconsin. This bill is supported by the Wisconsin Department of Veterans Affairs.
- This bill is important for epilepsy patients to maintain control of seizures and other unintentional therapy failures.
- Representative Musser and I have offered this bill on behalf of Wisconsin epilepsy patients, not to limit the dispensing of generic drugs, but to ensure that patients are notified of any change or substitution.
- The bill enjoys the support of the Epilepsy Foundation of Wisconsin along with the American Academy of Neurology.

Thank you for your consideration of my testimony. Please feel free to contact me if you have any questions or concerns.

Jon Erpenbach

Vote NO on Wisconsin S.B. 71

S.B. 71 Unnecessary -- Prescriber Already Has the Primary Authority

- S.B. 71 would require a pharmacist to obtain and document additional consent from the prescriber and patient prior to dispensing an antiepileptic generic drug product that has already been approved for substitution by the FDA.
- This mandate is unnecessary because the prescriber already has the primary authority, at the point of issuing a prescription order, to indicate whether a generic substitution is permitted.
- In fact, according to Wisconsin law, a pharmacist may not make a generic substitution if the prescriber indicates on the prescription that he/she wishes for the patient to take the brand medication. The prescriber has the option to specify in writing, or if a prescription is transmitted electronically, by designating in electronic format, the phrase "No substitutions," "N.S.," or words of similar meaning on the prescription.[1]

S.B. 71 Would Create Barriers to Patient Access to Generic Drugs

- The mandates in this bill would have a negative impact on patient care because of the unnecessary and burdensome steps both pharmacists and prescribers would have to take before patients could obtain their medications. This would take time away from both the pharmacist's and the prescriber's ability to serve the needs of their patients.
- A patient may have to unnecessarily wait for hours or even days for additional substitution approval if the mandates of S.B. 71 were enacted. Such delays in the delivery of medications, particularly for patients with strict medication regimes, such as patients with epilepsy, can have harmful and possibly life-threatening results.
- The requirements of S.B. 71 would create major logistical challenges to generic substitution that, in order to avoid delay, could leave pharmacists with no choice but to dispense more expensive brand-name drugs even if the patient prefers the equivalent generic drug product.
- Generic substitution, as permitted by current Wisconsin law, is a well-established practice and any unnecessary mandates would inhibit access to prescription drugs that provide significant cost-savings to consumers, health plans, and employers.

AMA and FDA Support Generic Substitution

- The American Medical Association (AMA) recently restated its policy with regard to generic substitution and looked specifically at the substitution of narrow therapeutic index (NTI) drugs (such as anticonvulsants). After reviewing the scientific evidence, the AMA's Council on Science and Public Health determined that a more stringent generic substitution process for NTI drugs was not necessary. The AMA's House of Delegates concurred with this determination.
- The U.S. Food and Drug Administration (FDA) also recently restated its policy on bioequivalence and the use of generic substitution with drugs listed in the FDA's "Orange Book." Specifically, the FDA stated that:
    - "Additional clinical tests or examinations by the health care provider are not needed when a generic drug product is substituted for the brand-name product.
    - Special precautions are not needed when a formulation and/or manufacturing change occurs for a drug product provided that the change is approved according to applicable laws and regulations by the FDA.
    - As noted in the 'Orange Book,' in the judgment of the FDA, products evaluated as therapeutically equivalent can be expected to have equivalent clinical effect whether the product is a brand-name or generic drug product.
    - It is not necessary for the health care provider to approach any one therapeutic class of drug products differently from any other class, when there has been a determination of therapeutic equivalence by FDA for the drug products under consideration."[2]
- **The FDA's policy applies to all FDA-approved generic drugs, including generic drugs used to treat epilepsy.**

Academy of Managed Care Pharmacy, American Pharmacists Association, Generic Pharmaceutical Association, National Alliance of State Pharmacy Associations, National Association of Chain Drug Stores, Pharmaceutical Care Management Association

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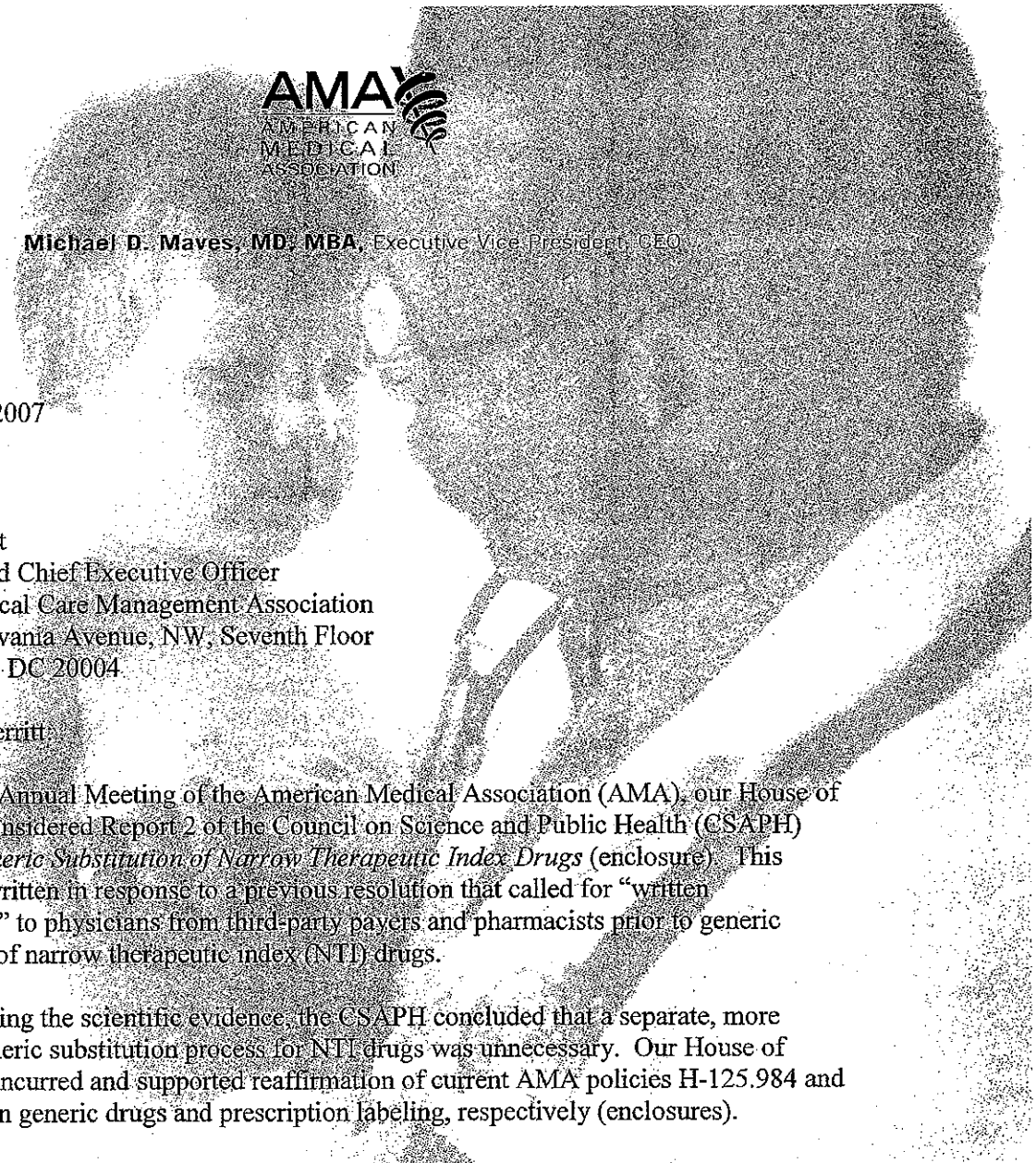
[1] Wis. Stat. § 450.13 (2006).

[2] Letter from the U.S. Food and Drug Administration (FDA) to National Association of Chain Drug Stores, (April 16, 2007); *see also* Letter from FDA to Iowa Pharmacy Association, (January 11, 2008).



AMA
AMERICAN MEDICAL ASSOCIATION

Michael D. Maves, MD, MBA, Executive Vice President, CEO

August 30, 2007

Mark Merritt
President and Chief Executive Officer
Pharmaceutical Care Management Association
601 Pennsylvania Avenue, NW, Seventh Floor
Washington, DC 20004

Dear Mr. Merritt:

At the 2007 Annual Meeting of the American Medical Association (AMA), our House of Delegates considered Report 2 of the Council on Science and Public Health (CSAPH) entitled, *Generic Substitution of Narrow Therapeutic Index Drugs* (enclosure). This report was written in response to a previous resolution that called for "written notifications" to physicians from third-party payers and pharmacists prior to generic substitution of narrow therapeutic index (NTI) drugs.

After reviewing the scientific evidence, the CSAPH concluded that a separate, more stringent generic substitution process for NTI drugs was unnecessary. Our House of Delegates concurred and supported reaffirmation of current AMA policies H-125.984 and H-115.994 on generic drugs and prescription labeling, respectively (enclosures).

Both our Council and our House also recommended that the AMA make third-party payer and pharmacy organizations aware of these policies and that is the purpose of this letter. In particular, I would like to call your attention to H-125.984[1], H-115.994[1], and H-115.994[4].

H-125.984[1] and H-115.994[1] express the AMA's position that the prescribing physician ultimately has the authority to select the generic or brand name drug, provided he/she appropriately designates a choice on the prescription that is consistent with state law. While the AMA recognizes that under most pharmacy benefit plans the patient co-pay will be substantially less for a generic drug, the prescribing physician still must make his/her drug selection decision in the best interests of the individual patient. We urge pharmacy benefit management companies (PBMs) to respect this authority.

H-115.994[4] addresses the AMA's concern about patient confusion when pharmacies change drug manufacturers at the time a generic prescription is refilled. While the AMA discourages this practice, we also recognize the reality that pharmacies will change manufacturers for various reasons. When this occurs, the AMA believes that a pharmacist has an obligation to inform the patient of the change in manufacturer – both orally and on the prescription bottle label – to minimize the potential for patient confusion. We urge PBMs to support this position in communications with its network pharmacies.

The AMA appreciates your attention to these issues.

Sincerely,

Michael D. Maves, MD, MBA

Enclosures (3)

REPORT 2 OF THE COUNCIL ON SCIENCE AND PUBLIC HEALTH (A-07)
Generic Substitution of Narrow Therapeutic Index Drugs
(Resolution 527, A-06)
(Reference Committee E)

EXECUTIVE SUMMARY

Objective: To review the evidence and the arguments surrounding the generic substitution of narrow therapeutic index (NTI) drugs.

Methods: Previous reports of this Council on generic drugs were reviewed. Published studies from 2002 through February 2007 were identified through a MEDLINE search of English-language articles, using the MeSH terms, "drugs, generic," and "therapeutic equivalency." A total of 103 articles were identified. Additional articles were identified by a review of references cited in these publications. In addition, the Web sites of the Food and Drug Administration (FDA) and various medical specialty societies were accessed for articles relevant to NTI drugs.

Results: Generic drugs are significantly less expensive than brand name innovator drugs and provide an opportunity to reduce spending on pharmaceuticals in the United States. The FDA considers generic drug products to be "therapeutically equivalent" to brand name innovator products if they are pharmaceutical equivalents and show bioequivalence in healthy volunteers; such products receive an "A-rating." The FDA applies the same approval criteria for NTI drugs, which the Agency calls "narrow therapeutic range" drugs. Some physicians remain concerned about generic substitution of NTI drugs because of small differences between therapeutic and toxic doses and the need for therapeutic drug concentration or pharmacodynamic monitoring. However, scientific evidence to support these concerns either does not exist or is extremely weak. In large part, studies reviewed and cited in this report suggest "AB-rated" generic NTI drugs were bioequivalent to their brand name innovator products in patients with diseases for which the drugs are indicated.

Conclusion: Consistent with current American Medical Association (AMA) Policy H-125.984(1) (AMA Policy Database), the prescribing physician should ultimately make the decision on whether to allow generic substitution of an NTI drug for an individual patient. Furthermore, as stated in current AMA Policy H-115.994(4), when a prescription for a generic drug product is refilled (e.g., for a patient with a chronic disease), changing the manufacturer should be discouraged, whenever possible, to avoid confusion for the patient. For many drugs, especially those with a narrow therapeutic range, therapeutic drug concentration or pharmacodynamic monitoring is necessary to assure the desired clinical response. Such monitoring is necessary irrespective of whether the drug is a brand name or generic product. In addition, patients must receive adequate education to be able to fully understand the nature and proper use of their medications.

Action of the AMA House of Delegates 2007 Annual Meeting: Council on Science and Public Health Report 2 Recommendations Adopted, and Remainder of Report Filed.

REPORT OF THE COUNCIL ON SCIENCE AND PUBLIC HEALTH

CSAPH Report 2-A-07

Subject: Generic Substitution of Narrow Therapeutic Index Drugs (Resolution 527, A-06)

Presented by: Mohamed K. Khan, MD, PhD, Chair

Referred to: Reference Committee E (Paul C. Matson, MD, Chair)

Resolution 527, introduced by the Georgia Delegation at the 2006 Annual Meeting and referred to the Board of Trustees, asks:

> That our American Medical Association (AMA) adopt a policy in support of the Centers for Medicare and Medicaid Services prohibiting any substitutions of a prescribed medication with a narrow therapeutic index with another manufacturer's form of the same medication with a narrow therapeutic index on a Medicare Part D Prescription Plan chosen by the patient, without first submitting written notification of such change by the formulary to the patient and the prescribing physician; and
>
> That our AMA request the Centers for Medicare and Medicaid Services produce guidelines prohibiting any substitution of physician prescribed medications with a narrow therapeutic index, as defined using the [Food and Drug Administration] requirements, from a certain manufacturer to any other manufacturer's form of that medication on a Medicare Part D Prescription Plan, without first submitting written notification of such change by the formulary to the patient and the prescribing physician.

At the 2002 Annual Meeting, this Council presented a report on generic drugs, which included a detailed discussion of the generic substitution of narrow therapeutic index (NTI) drugs.[1] The following report will provide an update of the earlier report with a focus on the evidence and the arguments surrounding the generic substitution of NTI drugs.

Methods

Previous reports of this Council on generic drugs were reviewed. Published studies from 2002 through February 2007 were identified through a MEDLINE search of English-language articles, using the MeSH terms, "drugs, generic," and "therapeutic equivalency." A total of 103 articles were identified. Additional articles were identified by a review of references cited in these publications. In addition, the Web sites of the Food and Drug Administration (FDA) and various medical specialty societies were accessed for articles relevant to NTI drugs.

Action of the AMA House of Delegates 2007 Annual Meeting: Council on Science and Public Health Report 2 Recommendations Adopted, and Remainder of Report Filed.

AMA Policies

AMA Policy H-125.984 (AMA Policy Database) is our AMA's primary policy on generic drugs, as follows:

"Our AMA believes that: (1) Physicians should be free to use either the generic or brand name in prescribing drugs for their patients, and physicians should supplement medical judgments with cost considerations in making this choice. (2) It should be recognized that generic drugs frequently can be less costly alternatives to brand-name products. (3) Substitution with Food and Drug Administration (FDA) "B"-rated generic drug products (i.e., products with potential or known bioequivalence problems) should be prohibited by law, except when there is prior authorization from the prescribing physician. (4) Physicians should report serious adverse events that may be related to generic substitution, including the name, dosage form, and the manufacturer, to the FDA's MedWatch program. (5) The FDA, in conjunction with our AMA and the United States Pharmacopoeia, should explore ways to more effectively inform physicians about the bioequivalence of generic drugs, including decisional criteria used to determine the bioequivalence of individual products. (6) The FDA should fund or conduct additional research in order to identify the optimum methodology to determine bioequivalence, including the concept of individual bioequivalence, between pharmaceutically equivalent drug products (i.e., products that contain the same active ingredient(s), are of the same dosage form, route of administration, and are identical in strength). (7) The Congress should provide adequate resources to the FDA to continue to support an effective generic drug approval process. (CSA Rep. 6, A-02)"

AMA Policy H-115.974 also is relevant to generic substitution and the dispensing of generic drug products, as follows:

"Our AMA recommends (1) That when a physician desires to prescribe a brand name drug product, he or she do so by designating the brand name drug product and the phrase "Do Not Substitute" (or comparable phrase or designation, as required by state law or regulation) on the prescription; and when a physician desires to prescribe a generic drug product, he or she do so by designating the USAN-assigned generic name of the drug on the prescription. (2) That, except where the prescribing physician has indicated otherwise, the pharmacist should include the following information on the label affixed to the container in which a prescription drug is dispensed: in the absence of product substitution, (a) the brand and generic name of the drug dispensed; (b) the strength, if more than one strength of drug is marketed; (c) the quantity dispensed; and (d) the name of the manufacturer or distributor. (3) When generic substitution occurs: (a) the generic name (or, when applicable, the brand name of the generic substitute ["branded" generic name]) of the drug dispensed; (b) the strength, if more than one strength of drug is marketed; (c) the quantity dispensed; (d) the manufacturer or distributor; and (e) either the phrase "generic for [brand name prescribed]" or the phrase "substituted for [brand name prescribed]". (4) When a prescription for a generic drug product is refilled (e.g., for a patient with a chronic disease), changing the manufacturer or distributor should be discouraged to avoid confusion for the patient; when this is not possible, the dispensing pharmacist should satisfy the following conditions: (a) orally explain to the patient that the generic drug product being dispensed is from a different manufacturer or distributor and, if possible (e.g., for solid oral dosage forms), visually show the product being dispensed to the patient; (b) replace the name of the prior generic drug manufacturer or distributor on the label affixed to the prescription drug container with the name of the new generic drug manufacturer or distributor and, show this to the patient; (c) affix to the primary label an auxiliary (sticker) label that states, "This is the same medication you have been getting. Color, size, or shape may appear different"; and (d) place a notation on the prescription record that contains the name of the new generic drug manufacturer

or distributor and the date the product was dispensed. (BOT Rep. 1, A-95; Amended: CSA Rep. 2, I-99; Modified Res. 512, I-00; Reaffirmed: CSA Rep. 6, A-02)"

Generic Drug Use and Costs

Generic drugs accounted for 56% of all prescriptions dispensed in the United States in 2005, but this represented less than 13% of every dollar spent on prescription drugs. The average retail price of a prescription for a generic drug was $29.82 versus $101.71 for a brand name drug.[2] Thus, the use of generic drugs provides an opportunity to substantially reduce spending on pharmaceuticals. For this reason, the Medicare Part D outpatient prescription drug program strongly encourages the use of generic drugs whenever possible, and the Centers for Medicare and Medicaid Services (CMS) reported that 61% of Part D prescriptions dispensed in the third quarter of 2006 were for generic drugs.[3]

Approval of Generic Drug Products

CSA Report 6 (A-02) provided an extensive discussion of this subject,[1] and the following is a synopsis of that discussion to provide context for the current report. Generic drug products are approved in the United States via the Abbreviated New Drug Application (ANDA) process. Generic products approved under an ANDA must be "pharmaceutical equivalents" (i.e., have the same active ingredient[s], route of administration, dosage form, and strength) of the reference drug (brand name innovator) product. They must also be "bioequivalent" and the manufacturer must supply other basic technical information related to manufacturing of the product that is normally required of any New Drug Application (NDA).[1,4]

Bioequivalence is defined as "the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents...becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study."[4,5] The FDA currently uses an "average bioequivalence" approach, which involves a comparison of means. For immediate-release oral dosage forms, the standard average bioequivalence determination employs a single-dose, two-way crossover study, typically conducted in a limited number of healthy volunteers (usually 24 to 36 adults). For drugs with long half-lives, parallel design studies may be used. Both the rate and extent of absorption are evaluated. The former includes the maximum plasma concentration (C_{max}) and the time required to achieve this value (T_{max}). The extent of absorption is measured by the area under the plasma concentration-time curve (AUC). Results are analyzed according to whether the generic product (test), when substituted for the brand name product (reference), is significantly less bioavailable, and alternatively, whether the brand name product, when substituted for a generic product, is significantly less bioavailable (the two 1-sided tests). The core of the bioequivalence concept is an "absence of a significant difference." A difference of >20% is viewed by the FDA as significant. By convention, all data are expressed as a ratio of the average response (AUC and C_{max}) for test/reference, so the limit expressed in the second analysis is 125% (reciprocal of 80%). Tests are carried out using an analysis of variance and calculating a 90% confidence interval (CI) for the average of each pharmacokinetic parameter, which must be entirely within the 80% to 125% boundaries.[1,4,5]

The FDA considers generic drug products to be "therapeutically equivalent" to brand name innovator products if they meet the criteria outlined above, even though other characteristics of the product (e.g., shape, color, excipients) may be different. Generic drug products that the FDA considers to be therapeutically equivalent to brand name innovator products are "A-rated," and those that are not therapeutically equivalent are "B-rated." These are the first letters of

therapeutic equivalence evaluation codes for all drug products listed in the FDA's publication, *Approved Drug Products with Therapeutic Equivalence Evaluations* (Orange Book).[4] A second letter follows the "A" or "B" rating and provides additional information on the basis for the FDA's evaluation. For example, most orally administered generic drug products that are therapeutically equivalent are designated with the code "AB," which means that actual or potential bioequivalence problems have been resolved with adequate in vivo and/or in vitro evidence supporting bioequivalence.[4]

Concerns have been raised as to whether assessment of bioequivalence assures therapeutic equivalence, and numerous case reports have appeared in the medical literature suggesting problems temporally related to generic substitutions with a number of "A-rated" products.[1] However, the FDA has investigated numerous reports of potential generic product inequivalence, and the Agency has claimed it cannot document a single example of therapeutic failure when an FDA-designated therapeutically equivalent product was substituted for its reference (brand name innovator) product.[1,6] The FDA also has conducted two large surveys to quantify the differences between generic and brand name products. The first, conducted on 224 bioequivalence studies submitted in approved applications during 1985 and 1986, found an average difference in AUC measures between reference and generic products of 3.5%.[7] The second, involving 127 bioequivalence studies submitted in 1997 found average differences of 3.47% for AUC and 4.29% for C_{max}.[8] Finally, it is important to emphasize that when the formulation of a brand name innovator drug product is changed by its manufacturer, not an infrequent occurrence, the identical bioequivalence tests are performed to show therapeutic equivalence.[1]

Generic Substitution of Narrow Therapeutic Index Drugs

Therapeutic Equivalence Considerations. There is no universally accepted definition of an NTI drug. The FDA prefers to use the term "narrow therapeutic range," but notes that "narrow therapeutic index" is more commonly used. In its most recent *Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products---General Considerations*, the FDA defines narrow therapeutic range drug products "as containing certain drug substances subject to therapeutic drug concentration or pharmacodynamic monitoring, and/or where product labeling indicates a narrow therapeutic range designation." Examples cited by the FDA include: digoxin, lithium, phenytoin, theophylline, and warfarin. While the FDA Guidance recommends that sponsors (manufacturers) consider additional testing and/or controls to ensure the quality of narrow therapeutic range drug products, the Guidance recommends that "the traditional bioequivalence limit of 80 and 125 percent for non-narrow therapeutic range drugs remain unchanged for the bioavailability measures (AUC and C_{max}) of narrow therapeutic range drugs."[5]

As discussed in CSA Report 6 (A-02), surveys and guidelines confirm that some physicians remain concerned about the potential therapeutic inequivalence of generic NTI products, including antiepileptic drugs, antiarrhythmics, warfarin, and cyclosporine.[1] These include current position statements of the: 1) American Academy of Neurology that: a) opposes generic substitution of anticonvulsant drugs for the treatment of epilepsy without the attending physician's approval; and b) opposes prior authorization requirements by public and private formularies for anticonvulsant drugs in the treatment of epilepsy[9]; and 2) American Association of Clinical Endocrinologists, The Endocrine Society, and the American Thyroid Association (joint statement) that: a) raises concerns with the FDA's method for determining bioequivalence for generic levothyroxine products; and b) recommends that physicians not substitute levothyroxine drug products.[10] Our AMA also has a policy directive (D-125.991) that urges the FDA to re-examine its bioequivalence standards for levothyroxine.

CSA Report 6 (A-02) contained a detailed discussion of both the evidence and the arguments surrounding the generic substitution of NTI drugs, including antiepileptic drugs, antiarrhythmic drugs, warfarin, and cyclosporine.[1] The current report briefly reviews the more recent (since 2002), but limited published studies that were conducted in the United States.

Antiepileptic Drugs. Based on a retrospective review of approximately 200 medical records of patients with seizures who had been mandated to switch from Dilantin Kapseals to an "AB-rated" generic phenytoin product (Mylan Pharmaceuticals) in State of Minnesota health plans without physician notification, eight adult patients were identified whose seizures increased such that they were switched back to the brand name product. Mean total phenytoin serum concentration on brand was 17.7 $\pm$ 5.3 mg/L, decreased to 12.5 $\pm$ 2.7 mg/L on generic, and increased to 17.8 $\pm$ 3.9 mg/L after brand was re-introduced. Unbound phenytoin serum concentrations decreased in each of the eight patients when switched to generic. This small observational study had obvious limitations, however.[11]

Antiarrhythmic Drugs. A retrospective chart review was performed on 138 patients with cardiac arrhythmias in a Veterans Administration (VA) Medical Center who were taking a stable dose of amiodarone before and after switching from Cordarone, the brand name innovator product, to an "AB-rated" generic product (Pacerone from Upsher-Smith Laboratories). For 77 patients who took each product at the same dose, steady-state plasma concentrations of amiodarone and its active metabolite, desethylamiodarone (DEA), did not differ among the two drug products. However, after substitution with the generic product, 11 patients experienced a large change of $\geq$100% in amiodarone concentrations. Because of limitations in the study design, it could not be definitively concluded that these changes were due to the change in drug formulation. Plasma concentrations of the active metabolite DEA were very stable after the switch, and no patient developed new clinical evidence of toxicity. The authors concluded that it is possible to switch amiodarone products with minimal risk to the vast majority of patients. Monitoring of drug concentrations in plasma is warranted.[12]

Warfarin. An anticoagulation clinic associated with an HMO collected data on 182 patients eight months prior to and 10 months after the substitution of an "AB-rated" generic warfarin product (Barr Laboratories) for Coumadin (brand name innovator product) for the following endpoints: 1) international normalized ratio (INR) control; 2) frequency of INR monitoring; 3) number of dose changes; and 4) rate of thrombotic and hemorrhagic events. No differences were found in any endpoint. The authors concluded that generic substitution of warfarin could be done safely without the need for additional monitoring.[13]

A nonprofit, group model HMO began a system-wide conversion of patients from Coumadin to an "AB-rated" generic warfarin product (Barr Laboratories). A retrospective study was done on 2,299 patients who had been taking warfarin for at least 180 days and who had received uninterrupted oral anticoagulation therapy during the 90 days before and 90 days after switching to generic warfarin. The primary endpoint was the calculated amount of time each patient's INR values were within the patient-specific target INR range in the 90 days before and after the switch. Data also were collected on adverse events and medical resource utilization, and a pharmacoeconomic analysis was performed. The overall difference in calculated time INR values was below (22.6% before vs. 26.1% after switch, p=0.0001) and within (65.9% before vs. 63.3% after switch, p=0.0002) the therapeutic INR range was statistically but not clinically significant. Only 28% of patients experienced a change in therapeutic INR control of 10% or less, 33.1% experienced INR control that improved by greater than 10%, and 38.9% experienced INR control that worsened by more than 10%. The INR control varied by greater than 50% after product conversion in 13% of patients. Whether this variability in anticoagulation response was

directly attributable to generic substitution or simply reflects the inherent variability associated with warfarin therapy could not be determined. No statistically significant difference was noted in the number of nonfatal anticoagulation-related adverse events after generic substitution, and the proportion of patients who actually experienced adverse events was small. However, the study design prevented analysis of adverse events that necessitated withdrawal of patients from the study. The difference in total treatment costs associated with brand name and generic warfarin was $3,128/100 person-years in favor of the generic product. The authors concluded that most patients were successfully switched from brand name to generic warfarin. The authors also recommended that additional INR monitoring should occur in the days and weeks after generic substitution of warfarin products.[14]

Cyclosporine. An open-label, three-period design, multicenter study was performed in 50 renal transplant recipients taking stable doses of Neoral, the brand name innovator cyclosporine product. Patients continued on their Neoral regimen during period I (days 1-14), switched to the same dosage of an "AB-rated" generic cyclosporine product (Gengraf from Abbott Laboratories) during period II (days 15-28), and switched back to the same dosage of Neoral during period III (days 29-35). Twelve-hour pharmacokinetic evaluations (maximum observed blood concentration [C_{max}], concentration before dosing [C_{trough}], time to maximum observed concentration [T_{max}], and area under the blood concentration-vs.-time curve [AUC]) occurred on days 1, 14, 15, 28, and 29. Predose C_{trough} samples also were evaluated on days 7, 21, and 35; laboratory and safety parameters also were evaluated. The pharmacokinetics of the generic drug product (C_{max}, T_{max}, C_{trough}, and AUC) were indistinguishable from the Neoral values in these stable renal transplant patients, and the bioequivalent capsules were interchangeable with respect to C_{max}, C_{trough}, and AUC at steady state and also on conversion from one capsule formulation to another. The 90% confidence intervals for the generic vs. Neoral comparison at steady state (day 28 vs. day 14) were 0.95 to 1.03 for AUC and 0.92 to 1.04 for C_{max}. Trough concentrations remained consistent throughout the study with no need for dosage adjustment in any patient, and no differences in adverse events were observed. The authors concluded that the "AB-rated" generic drug product was interchangeable with Neoral in stable renal transplant patients.[15]

Forty-one patients receiving follow-up care at a renal transplant clinic in the VA healthcare system were switched from Neoral to an "AB-rated" generic cyclosporine product (Gengraf from Abbott Laboratories) based on a 1:1 dosing equivalency. Steady state cyclosporine trough concentrations were obtained both prior to and following the generic substitution. Patients also were monitored for changes in serum creatinine, hospitalization, cyclosporine toxicity, graft rejection, and need for further adjustment in cyclosporine regimen. No differences in cyclosporine trough concentrations or serum creatinine were observed following the Neoral to generic conversion. There were no reports of cyclosporine toxicity, no episodes of graft rejection, and no need for further dosage adjustment related to generic substitution. The authors concluded that the "AB-rated" generic drug product was interchangeable with Neoral in these renal transplant patients.[16]

Among 82 stable renal transplant patients being treated with Neoral on the renal transplant unit of a county medical center, 73 patients were switched to an "AB-rated" generic cyclosporine product (Gengraf from Abbott Laboratories) based on a 1:1 dosing equivalency. Nine patients remained on Neoral. Cyclosporine trough concentrations and serum creatinine concentrations were measured prior to and at two and four weeks following the generic substitution. Thirteen of 73 patients who switched to the generic drug required a dosage adjustment after the mean cyclosporine trough concentrations changed from 234 $\pm$ 96 ng/ml at baseline to 289 $\pm$ 102 ng/ml at two weeks. None of nine patients who remained on Neoral required a dosage adjustment. No significant differences in serum creatinine concentrations were observed in either group of

patients. The authors recommended additional drug monitoring when there is generic substitution of cyclosporine.[17]

Clinical outcomes were compared for de novo kidney transplant recipients who received either Neoral (n=100) or an "AB-rated" generic cyclosporine product (Gengraf from Abbott Laboratories) (n=88) in a single-center, retrospective review. When compared to patients who received Neoral, patients who received the generic cyclosporine product were significantly more likely to have an acute rejection episode (39% vs. 25%, p=0.04), more likely to have a second rejection episode (13% vs. 4%, p=0.03), or to have received an antibody preparation to treat acute rejection (19% vs. 8%, p=0.02). Patients treated with the generic drug had a higher degree of intrapatient variability for cyclosporine trough concentrations as determined by % coefficient of variation (%CV) ($p<0.05$). The authors concluded that the incidence of acute rejection post-transplant was significantly higher in patients who received the generic drug when compared to Neoral, and they recommended that a larger, prospective controlled clinical trial be conducted to confirm their findings.[18]

Levothyroxine. No published studies on the generic substitution of levothyroxine in patients with hypothyroidism were found in the CSAPH's search of the literature since 2002.

A potential concern regarding generic substitution of levothyroxine sodium is that there are four reference (brand name innovator) products, Unithroid, Synthroid, Levoxyl, and Levothroid, and three-character codes, AB1, AB2, AB3, and AB4, respectively, are assigned to each of these products in the FDA's Orange Book. Generic drug products may be determined by the FDA to be therapeutically equivalent to one or more of these reference products, and the reference products, themselves, may be bioequivalent to one another. For example, Synthroid (AB1, AB2) is considered to be therapeutically equivalent to Unithroid, but not to Levoxyl and Levothroid. Generic levothyroxine sodium made by GenPharm (AB2, AB3) is considered to be therapeutically equivalent to Synthroid and Levoxyl, but not to Unithroid or Levothroid. On the other hand, generic levothyroxine sodium made by Mylan (AB1, AB2, AB3, AB4) is considered to be therapeutically equivalent to all four reference products, even though some reference products are not considered to be therapeutically equivalent to each other. Listings of levothyroxine sodium products consume 20 pages of the FDA's Orange Book.[4] This has the potential to result in considerable confusion regarding appropriate generic substitution among these products in the outpatient practice environment.[10]

Other Patient Safety Considerations. The frequency of medication errors and preventable medication-related injuries represents a very serious cause for concern. Medication errors can occur at any point in the medication use process and in any care setting.[19] While the focus usually has been on errors caused by healthcare professionals, there is substantial evidence that patient errors also are important, whether they are due to non-adherence (non-compliance) with medication regimens,[20] inappropriate use of medications,[21] or an inability to understand simple information, such as prescription drug labels.[22]

In a report of this Council entitled, "Labeling of Prescription Drug Containers for Generic-Substituted Drugs" (CSA Report 2, I-99), it was recognized that the potential also exists for patient confusion when a generic drug is substituted for a brand name drug, or when a pharmacist changes the manufacturer of the generic drug during a refill. For example, the drug names (brand vs. generic) and/or the color, shape, and markings of solid oral dosage forms may be different.[23] AMA Policy H-115.974 (see above) has two recommendations that are intended to minimize this problem. State generic substitution laws allow physicians to designate "Do Not Substitute" (or a comparable phrase or designation) on a prescription, thus allowing the physician to decide if a

generic drug product can be substituted. AMA Policy H-115.974(1) recommends that physicians exercise this authority and clearly designate their preference when prescribing multisource drugs where alternative generic products are available. AMA Policy H-115.974(4) also discourages pharmacies from changing generic manufacturers when any generic prescription is refilled, and it lays out recommendations for pharmacists to educate patients if this cannot be avoided. Because of the potential for a disastrous outcome if there is a problem with the generic substitution of an NTI drug, these recommendations are especially applicable.

Conclusion

Generic drugs are significantly less expensive than brand name innovator drugs and provide an opportunity to reduce spending on pharmaceuticals in the United States. While physicians should be free to use either the generic or brand name in prescribing drugs for their patients, physicians should supplement medical judgments with cost considerations in making this choice (AMA Policy H-125.984).

As previously discussed in CSA Report 6 (A-02), the criteria used by the FDA to ensure bioequivalence among multisource drug products are widely misunderstood. These criteria do not allow for -20% to +25% difference in bioavailability between products. Rather, these parameters represent the statistical universe in which measures of variance must reside. In practice, the mean differences in pharmacokinetic parameters for most orally administered generic drug products are closer to 3% or 4%.[1,7,8]

The FDA is confident that its methodology for approving generic drugs, including NTI drugs, is adequate to establish therapeutic equivalence. The Agency has claimed it cannot document a single example of therapeutic failure when an FDA-designated therapeutically equivalent product was substituted for its reference (brand name innovator) product.[1,6] Furthermore, the same criteria for bioequivalence are applied to brand name products when they undergo formulation changes. Like generic drugs, these reformulated brand name products are never tested in a clinical population.

While concerns still persist among some physicians about the therapeutic equivalence of generic NTI drugs to their brand name innovator products, scientific evidence to support these concerns either does not exist or is extremely weak. In large part, studies reviewed and cited in this report suggest "AB-rated" generic NTI drugs were bioequivalent to their brand name innovator products in patients with diseases for which the drugs are indicated. Theoretical assumptions of the possibility of inequivalence are not a sufficient basis for presuming its presence and acting on that assumption. Anecdotal reports are similarly unhelpful, since one is often unable to distinguish product failure from a natural change in disease process or patient response. Consistent with current AMA Policy H-120.984, however, physicians should continue to report serious adverse events that may be related to generic substitution to the FDA's MedWatch program, and the FDA should continue to pursue research to ensure the methodology to determine bioequivalence is optimal.

Given the present evidence on the therapeutic equivalency of all FDA "A-rated" drugs, including those with a narrow therapeutic range, the prescribing physician should be able to decide whether a specific brand or generic drug product is most appropriate for the individual patient. Consistent with state laws, third-party payers should not substitute a generic for brand name drug unless it has been authorized by the prescribing physician. As stated in current AMA Policy H-115.994, when a prescription for a generic drug product is refilled (e.g., for a patient with a chronic

disease), changing the manufacturer should be discouraged, whenever possible, to avoid confusion for the patient.

For many drugs, especially those with a narrow therapeutic range, therapeutic drug concentration or pharmacodynamic monitoring is necessary to assure the desired clinical response. Such monitoring is necessary irrespective of whether the drug is a brand name or generic product. In addition, patients must receive adequate education to be able to fully understand the nature and proper use of their medications. As described in current AMA Policy H-115.974, this should include appropriate education from the pharmacist if the generic drug manufacturer is changed when the prescription is refilled.

RECOMMENDATIONS

The Council on Science and Public Health recommends that the following recommendations be adopted in lieu of Resolution 527 (A-06) and that the remainder of this report be filed:

1. That American Medical Association (AMA) Policies H-125.984 and H-115.974 be reaffirmed. (Reaffirm HOD Policy)

2. That our AMA inform the Centers for Medicare and Medicaid Services, America's Health Insurance Plans, the Pharmaceutical Care Management Association, the National Association of Boards of Pharmacy, the National Association of Chain Drug Stores, the National Community Pharmacists Association, and the American Pharmacists Association about AMA Policies H-125.984 and H-115.974, and that our AMA urge these payer and pharmacy organizations to support these AMA policies. (Directive to Take Action)

Fiscal Note: $500

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H-125.984 Generic Drugs

Our AMA believes that:

(1) Physicians should be free to use either the generic or brand name in prescribing drugs for their patients, and physicians should supplement medical judgments with cost considerations in making this choice.

(2) It should be recognized that generic drugs frequently can be less costly alternatives to brand-name products.

(3) Substitution with Food and Drug Administration (FDA) "B"-rated generic drug products (i.e., products with potential or known bioequivalence problems) should be prohibited by law, except when there is prior authorization from the prescribing physician.

(4) Physicians should report serious adverse events that may be related to generic substitution, including the name, dosage form, and the manufacturer, to the FDA's MedWatch program.

(5) The FDA, in conjunction with our AMA and the United States Pharmacopoeia, should explore ways to more effectively inform physicians about the bioequivalence of generic drugs, including decisional criteria used to determine the bioequivalence of individual products.

(6) The FDA should fund or conduct additional research in order to identify the optimum methodology to determine bioequivalence, including the concept of individual bioequivalence, between pharmaceutically equivalent drug products (i.e., products that contain the same active ingredient(s), are of the same dosage form, route of administration, and are identical in strength).

(7) The Congress should provide adequate resources to the FDA to continue to support an effective generic drug approval process. (CSA Rep. 6, A-02)

H-115.974 Prescription Labeling

Our AMA recommends:

(1) That when a physician desires to prescribe a brand name drug product, he or she do so by designating the brand name drug product and the phrase "Do Not Substitute" (or comparable phrase or designation, as required by state law or regulation) on the prescription; and when a physician desires to prescribe a generic drug product, he or she do so by designating the USAN-assigned generic name of the drug on the prescription.

(2) That, except where the prescribing physician has indicated otherwise, the pharmacist should include the following information on the label affixed to the container in which a prescription drug is dispensed: in the absence of product substitution, (a) the brand and generic name of the drug dispensed; (b) the strength, if more than one strength of drug is marketed; (c) the quantity dispensed; and (d) the name of the manufacturer or distributor.

(3) When generic substitution occurs: (a) the generic name (or, when applicable, the brand name of the generic substitute ["branded" generic name]) of the drug dispensed; (b) the strength, if more than one strength of drug is marketed; (c) the quantity dispensed; (d) the manufacturer or distributor; and (e) either the phrase "generic for [brand name prescribed]" or the phrase "substituted for [brand name prescribed]".

(4) When a prescription for a generic drug product is refilled (e.g., for a patient with a chronic disease), changing the manufacturer or distributor should be discouraged to avoid confusion for the patient; when this is not possible, the dispensing pharmacist should satisfy the following conditions: (a) orally explain to the patient that the generic drug product being dispensed is from a different manufacturer or distributor and, if possible (e.g., for solid oral dosage forms), visually show the product being dispensed to the patient; (b) replace the name of the prior generic drug manufacturer or distributor on the label affixed to the prescription drug container with the name of the new generic drug manufacturer or distributor and, show this to the patient; (c) affix to the primary label an auxiliary (sticker) label that states, "This is the same medication you have been getting. Color, size, or shape may appear different;" and (d) place a notation on the prescription record that contains the name of the new generic drug manufacturer or distributor and the date the product was dispensed. (BOT Rep. 1, A-95; Amended: CSA Rep. 2, I-99; Modified Res. 512, I-00; Reaffirmed: CSA Rep. 6, A-02)

PBM Savings and Pharmacy Access In Wisconsin

Pharmacy benefit managers (PBMs) help make prescription drugs safer and more affordable for the vast majority of Americans by managing drug coverage provided by large employers, unions, health plans, Medicare Part D, and FEHBP, and other programs. PBMs pool the purchasing ability of more than 210 million consumers in order to negotiate substantial discounts from drug manufacturers and pharmacies. Conducting business in all 50 states, PBMs contract with nearly all retail pharmacies in the country and also employ thousands of in-house pharmacists to provide consumers widespread access to convenient drug store and mail-service pharmacy options.

PBMs in Wisconsin[1]

- In 2008, PBMs will manage prescription drug benefits for an estimated **4,478,000 people** in Wisconsin.
- Next year, PBMs will save Wisconsin consumers and employers a projected **$1.5 billion** on the cost of their prescription drugs.
- Over the next ten years, PBMs will save Wisconsin consumers and employers a projected **$21.6 billion** on the cost of their prescription drugs.

Pharmacy Access in Wisconsin[2]

PBMs spur competition among pharmacies which helps lower drug benefit costs for employers and consumers. Any pharmacy that accepts private insurance payments is likely part of a PBM pharmacy network. Thanks to PBMs, insured consumers can typically obtain their medication for a set copayment and need not worry about comparison shopping or filing an insurance claim. PBMs also work in the background to provide pharmacists with coverage information, flag potential problems like drug-to-drug interactions, and reimburse pharmacies for drug ingredient and dispensing costs. In Wisconsin today, consumers enjoy widespread access to a range of competing pharmacy options:

- In *urban* Wisconsin, consumers patronizing independent pharmacies have access to 11 competing pharmacies within two miles of their current pharmacy.
- In *suburban* Wisconsin, independent pharmacy consumers have access to 4 competing pharmacies located within 5 miles of their current pharmacy.
- Independent pharmacy consumers in *rural* Wisconsin typically have access to 8 competing pharmacies located with 15 miles of their current pharmacy.

[1] Data on PBM Savings as estimated by PricewaterhouseCoopers in their March 2007 report "Pharmacy Benefit Management Savings in Medicare and the Commercial Marketplace & the Cost of Proposed PBM Legislation, 2008-2017," available at pcmanet.org

[2] Data on pharmacy access as tabulated by SK&A Healthcare Information Solutions in their May 2007 report "Consumer Access to Pharmacies in the United States, 2007," available at pcmanet.org. Distances to competing urban, suburban, and rural pharmacies based on Medicare pharmacy network adequacy standards.

Barriers to Generic Substitution Negatively Impact Patient Care

Legislation Unnecessary -- Prescriber Already Has the Primary Authority

- This legislation would require a pharmacist to obtain additional consent from the prescriber and patient prior to dispensing an antiepileptic generic drug product that has already been approved for substitution by the FDA.
- This mandate is unnecessary because the prescriber already has the primary authority, at the point of issuing a prescription order, to indicate whether a generic substitution is permitted.
- In fact, according to most state laws, the pharmacist may not make a generic substitution if the prescriber indicates on the prescription that he/she wishes for the patient to take the brand medication. The prescriber has the option to write in his/her own handwriting on the prescription either "dispense as written" or "d.a.w.," or a similar notation, as directed by state law.

Mandates Create Barriers to Patient Access to Generic Drugs

- The mandates in this legislation would have a negative impact on patient care because of the unnecessary and burdensome steps both pharmacists and prescribers would have to take before patients could obtain their medications. This would take time away from both the pharmacist's and the prescriber's ability to serve the needs of their patients.
- A patient may have to unnecessarily wait for hours or even days for additional substitution approval if this legislation were enacted. Such delays in the delivery of medications, particularly for patients with strict medication regimes, such as patients with epilepsy, can have harmful and possibly life-threatening results.
- The requirements of this legislation would create major logistical challenges to generic substitution that, in order to avoid delay, could leave pharmacists with no choice but to dispense more expensive brand-name drugs even if the patient prefers the equivalent generic drug product.
- Generic substitution, as permitted by current state law, is a well-established practice and any unnecessary mandates would inhibit access to prescription drugs that provide significant cost-savings to consumers, health plans, and employers.

AMA and FDA Support Generic Substitution

- The American Medical Association (AMA) recently restated its policy with regard to generic substitution and looked specifically at the substitution of narrow therapeutic index (NTI) drugs (such as anticonvulsants). After reviewing the scientific evidence, the AMA's Council on Science and Public Health determined that a more stringent generic substitution process for NTI drugs was not necessary. The AMA's House of Delegates concurred with this determination.
- The U.S. Food and Drug Administration (FDA) also recently restated its policy on bioequivalence and the use of generic substitution with drugs listed in the FDA's "Orange Book." Specifically, the FDA stated that:
    - "Additional clinical tests or examinations by the health care provider are not needed when a generic drug product is substituted for the brand-name product.
    - Special precautions are not needed when a formulation and/or manufacturing change occurs for a drug product provided that the change is approved according to applicable laws and regulations by the FDA.
    - As noted in the 'Orange Book,' in the judgment of the FDA, products evaluated as therapeutically equivalent can be expected to have equivalent clinical effect whether the product is a brand-name or generic drug product.
    - It is not necessary for the health care provider to approach any one therapeutic class of drug products differently from any other class, when there has been a determination of therapeutic equivalence by FDA for the drug products under consideration." [1]
- **The FDA's policy applies to all FDA-approved generic drugs, including generic drugs used to treat epilepsy.**

Academy of Managed Care Pharmacy, American Pharmacists Association, Generic Pharmaceutical Association, National Alliance of State Pharmacy Associations, National Association of Chain Drug Stores, Pharmaceutical Care Management Association

[1] Letter from the U.S. Food and Drug Administration to National Association of Chain Drug Stores, (April 16, 2007).

ISSUE BRIEF

RESTRICTING GENERIC SUBSTITUTION OF DRUGS TO TREAT EPILEPSY

Academy of Managed Care Pharmacy

American Pharmacists Association

Generic Pharmaceutical Association

National Alliance of State Pharmacy Associations

National Association of Chain Drug Stores

Pharmaceutical Care Management Association

Introduction

Pharmacist substitution of Food and Drug Administration (FDA)-approved therapeutically equivalent generic medications for brand-name medications improves patient access while saving money for consumers, employers, and insurance carriers. Generic substitution is a legal and well-established practice throughout the country. Prescribers, when issuing prescriptions to patients, indicate whether a pharmacist may not engage in generic substitution, usually by marking the prescription order "dispense as written" or "brand necessary" as required by state law. Prescribers retain the ultimate authority in this matter.

Legislation is being proposed in a number of states that would create obstacles to existing generic substitution practices for prescription drugs used to treat epilepsy (known as "anticonvulsants"). This legislation would require pharmacists, when presented with a prescription order that is not marked "dispense as written" or "brand necessary," to obtain additional permission from both the prescriber and the patient before substituting a generic for the brand-name product. Some of these bills go even further by requiring pharmacists to maintain written documentation of the contact between themselves and the prescriber. We believe such mandates would adversely affect the delivery of patient care.

Prescribers Retain the Ultimate Authority

These bills create unnecessary and redundant requirements for prescribers and pharmacists. When prescribers issue a prescription order, they make an affirmative determination whether generic substitution is appropriate and that decision is indicated by what appears on the face of the prescription order. By not marking the prescription order "dispense as written" or "brand necessary," the prescriber has expressed permission to allow generic substitution; there is no benefit or improvement in care achieved by requiring a pharmacist to contact a prescriber to obtain further confirmation of consent. The additional work generated by legislation of this type would be duplicative of the consent already given via the original prescription order.

Proposals Would Create Negative Consequences for Patients

Such proposals would dramatically reduce patient access to prescription medications that provide significant cost-savings to consumers, health plans, and employers. In addition to creating barriers to the delivery of care, the proposed new process would pull prescribers and pharmacists away from their patients to comply with all the added requirements. Serious logistical problems may arise if pharmacists are required to obtain additional consent and the prescriber is not immediately reachable. As a result, patients may have to wait hours or even days to have their prescriptions filled. Such delays are both an inconvenience to patients and an impediment to the timely delivery of patient care. Patients with epilepsy, who must comply with a strict medication regime, would be particularly impacted by delays in drug therapy that can have immediate and serious health consequences.

Considering there are numerous FDA-approved *and* off-label uses of anticonvulsants, this further complicates the issue of obtaining additional consent to generically substitute drugs specifically for the treatment of epilepsy. Just because a patient is treated with an anticonvulsant drug does not mean that particular patient is epileptic. Unfortunately, prescribers rarely indicate the diagnosis on the prescription. Therefore, it is not possible for a pharmacist, based on a single prescription order, to determine whether the medication prescribed is to treat epilepsy. The only way that a pharmacist could ensure that he or she is meeting the proposed mandate would be by obtaining additional consent for every anticonvulsant prescribed, in addition to any other drug that could potentially be used to treat epilepsy, regardless of whether the patient is actually epileptic. This is an unworkable requirement that would cause extreme delays in the delivery of pharmacy care.

Conflicts with Medicaid Laws

These proposed mandates are also inconsistent with Medicaid laws relating to generic substitution. Medicaid programs generally require pharmacists to automatically dispense generically equivalent products if prescribers do not expressly indicate on the prescription face that a brand product is medically necessary. In a case where a prescriber has not indicated that a brand product is necessary, and the pharmacist is unable to obtain additional consent from the prescriber, the pharmacist would be forced to either violate Medicaid requirements or the state generic substitution laws if this type of legislation was enacted. For this reason, legislative mandates creating barriers to the safe and cost-saving practice of generic substitution are unworkable and poor public policy.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

January 11, 2008

Ms. Nicole Schultz
Iowa Pharmacy Association
8515 Douglas Avenue, Suite 16
Des Moines, IA 50322

Dear Ms. Schultz:

This is in reply to your correspondence dated November 6, 2007, directed to Ms. Susan Winckler requesting that the FDA provide a statement regarding generic substitution, particularly with respect to anti-epilepsy drugs. It was forwarded to the Office of Generic Drugs for a reply.

The FDA has many years of experience in the review of generic drugs and assures the quality and equivalence of approved generic drug products. FDA works with pharmaceutical companies to assure that all drugs marketed in the U.S., both brand-name and generic, meet specifications for identity, strength, quality, purity and potency. In approving a generic drug product, the FDA requires that the proposed generic product is demonstrated to be equivalent to the brand-name drug in both the rate and extent of absorption. As noted in the Preface to the *Approved Drug Products with Therapeutic Equivalence Evaluations* ("Orange Book") (27th Edition),

> FDA classifies as therapeutically equivalent those products that meet the following criteria: (1) they are approved as safe and effective; (2) they are pharmaceutical equivalents in that they (a) contain identical amounts of the same active drug ingredient in the same dosage form and route of administration, and, (b) meet compendial or other applicable standards of strength, quality, purity, and identity; (3) they are bioequivalent; (4) they are adequately labeled; (5) they are manufactured in compliance with Current Good Manufacturing Practice regulations.
>
> FDA considers drug products to be therapeutically equivalent if they meet the criteria outlined above, even though they may differ in certain other characteristics such as shape, scoring configuration, release mechanisms, packaging, excipients (including colors, flavors, preservatives), expiration date/time and other minor aspects of labeling (e.g., the presence of specific pharmacokinetic information) and storage conditions. When such differences are important in the care of a particular patient, it may be appropriate for the prescribing physician to require that a particular brand be dispensed as a medical necessity. With this limitation, however, FDA believes that products classified as therapeutically equivalent will produce the same clinical effect and safety profile as the prescribed product.

FDA is aware that certain individuals and groups have expressed particular concern about the switching of anti-epileptic drug products. To date, we have no scientific evidence that demonstrates a particular problem with this group of products. Further, there are frequently circumstances other than the switch that may cause untoward responses. We continue to follow-up such reports and interact with those concerned.

If FDA has determined a generic to be therapeutically equivalent to the innovator product, FDA continues to believe that:

- Additional clinical tests or examinations by the healthcare provider are not needed when a generic drug product is substituted for the brand-name product or vice-versa.
- Special precautions are not needed when a formulation or manufacturing change occurs for a drug product provided the change is approved according to applicable laws and regulations by the FDA.
- As noted in the "Orange Book," in the judgment of the FDA, products evaluated as therapeutically equivalent can be expected to have equivalent clinical effects whether the products are brand-name or generic.
- It is not necessary for the healthcare provider to approach any one therapeutic class of drug products differently from any other class when there has been a determination of therapeutic equivalence by FDA for the drug products under consideration.

We continue to monitor, take seriously, and, if indicated, investigate reports of potential inequivalence of all generic drugs. The FDA is committed to approving high-quality generic drug products that can be used with confidence by the American public.

Sincerely,

Gary Buehler, R.Ph.
Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration

cc: S. Winckler
C. Jung

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

April 16, 2007

National Association of
Chain Drug Stores
413 North Lee Street
P.O. Box 1417-D49
Alexandria, VA 22313-1480

This is in reply to your letter dated March 15, 2007 requesting that the FDA restate its policy regarding the bioequivalence and substitutability of drugs that are listed in the FDA's "Orange Book" or *Approved Drug Products with Therapeutic Equivalence Evaluations*.

The FDA has many years of experience in the review of generic drugs, and has great confidence in the quality and equivalence of generic drug products. FDA works with pharmaceutical companies to assure that all drugs marketed in the U.S., both brand-name and generic, meet specifications for identity, strength, quality, purity and potency. In approving a generic drug product, the FDA requires many rigorous tests and procedures to assure that the generic drug is interchangeable with the brand-name drug under all approved indications and conditions of use. As noted in the Preface to the Orange Book (27th Edition).

> FDA classifies as therapeutically equivalent those products that meet the following criteria: (1) they are approved as safe and effective; (2) they are pharmaceutical equivalents in that they (a) contain identical amounts of the same active drug ingredient in the same dosage form and route of administration, and (b) meet compendial or other applicable standards of strength, quality, purity, and identity; (3) they are bioequivalent; (4) they are adequately labeled; (5) they are manufactured in compliance with Current Good Manufacturing Practice regulations.
>
> FDA considers drug products to be therapeutically equivalent if they meet the criteria outlined above, even though they may differ in certain other characteristics such as shape, scoring configuration, release mechanisms, packaging, excipients (including colors, flavors, preservatives), expiration date/time and other minor aspects of labeling (e.g., the presence of specific pharmacokinetic information) and storage conditions. When such differences are important in the care of a particular patient, it may be appropriate for the prescribing physician to require that a particular brand be dispensed as a medical necessity. With this limitation, however, FDA believes that products classified as therapeutically equivalent will produce the same clinical effect and safety profile as the prescribed product.

If FDA has determined a generic to be therapeutically equivalent to the innovator product, FDA continues to believe, as stated in a letter dated January 28, 1998, to Health Practitioners, that:

- Additional clinical tests or examinations by the health care provider are not needed when a generic drug product is substituted for the brand-name product.
- Special precautions are not needed when a formulation and/or manufacturing change occurs for a drug product provided that the change is approved according to applicable laws and regulations by the FDA.
- As noted in the "Orange Book," in the judgment of the FDA, products evaluated as therapeutically equivalent can be expected to have equivalent clinical effect whether the product is a brand-name or generic drug product.
- It is not necessary for the health care provider to approach any one therapeutic class of drug products differently from any other class, when there has been a determination of therapeutic equivalence by FDA for the drug products under consideration.

We continue to monitor and, if indicated, investigate reports of potential inequivalence. The FDA is committed to approving high quality generic drug products that can be used with confidence by the American public.

Sincerely,

Steven Galson

Steven Galson, M.D.

EPILEPSY FOUNDATION
CENTRAL AND NORTHEAST WISCONSIN
Not another moment lost to seizures

Headquarters
1004 First Street • Stevens Point, WI 54481-2627

Cynthia Piotrowski
Executive Director
Epilepsy Foundation Central & Northeast Wisconsin
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- We see health care trends in the problem calls we receive from clients
- Clients are calling when they get home and they don't recognize the medications that have been dispensed
- The Epilepsy Foundations in Wisconsin would like to enlist pharmacists as an important treatment partner and insure that before any kind of substitution is made at the point of sale the patient and the physician are in the loop
- The American Academy of Neurology & the American Epilepsy Society have charged their members with filing Food & Drug Administration Medwatch reports about adverse incidents. A recent poll suggests that only 13% of neurologists have done so, but this is because neurologists currently have no way of knowing when these substitutions are made
- ~~AB 150~~ SB 71 insures that physicians will be able to adjust doses, order blood levels or monitor their patients as necessary when substitutions are made
- EF clients want cheaper co-pays and they want medications that are affordable – just like everyone else
- ~~AB 150~~ SB 71 insures that they can have confidence in generics and that their physicians will take steps when their formulation changes due to inconsistency of supply
- EF stresses that this is not anti-generic and we are not asking for pharmacists to absorb any costs. What we are doing is asking that they help make sure all parties involved are informed when changes are made by keeping in mind that epilepsy patients often have a very narrow therapeutic range.

On November 14th, my staff was notified by my doctor's office that on the 15th of November, the insurance company was no longer going to cover my Trileptal, but instead put me on Oxcarbazepine (a generic of Trileptal) due to cost. Within 24 hours, I had a seizure. I had been seizure free before that since July. Over the next nine days, I had 19 seizures.

I have had trouble with generic medications in the past and I feel that insurance companies should not be able to change medications from brand names to generics without consulting the patient first.

Once the seizures started, my doctor's office, the pharmacy, my staff and I all contacted the insurance company to let them know what was happening. The insurance company representative told my staff that I had to try two different generics and fail on both of them before they would put me back on the Trileptal. It felt to me like the insurance company did not care that I was suffering because of their decision.

On November 22nd, Thanksgiving Day, I was on a home visit and had a seizure. I had actually stopped breathing and my skin was a bluish/purple color. I was so wiped out that I had to go back to the group home early. The seizures are very, very hard on me. They leave me weak, confused and extremely tired.

My opinion is that the insurance company wasn't concerned with me as a person but was more interested in saving a few bucks at my expense.

Kyle Glamann
617 Hamilton St
Wausau WI 54403

distr. by Rep. Markey

THE WALL STREET JOURNAL. ONLINE

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PAGE ONE

PILL PUSH

Industry Fights Switch To Generics for Epilepsy

Big Drug Makers Help Patient Groups Lobby; More Attention to States

By SARAH RUBENSTEIN
July 13, 2007

In state legislatures across the country, the Epilepsy Foundation has been campaigning for bills that would make it harder for pharmacists to switch patients to inexpensive generic epilepsy pills. The effort is getting behind-the-scenes support from drug companies -- a sign of how the industry, long a potent lobbying force in Washington, is increasingly looking to states to achieve its goals.

The foundation, a nonprofit group supported by the drug industry, says switching to generics could cause dangerous seizures. The Food and Drug Administration says it hasn't seen persuasive evidence for that, and it believes each generic is equivalent to the brand-name drug it copies.

GENERIC DEBATE

- **The Situation:** The Epilepsy Foundation, helped by drug makers, is backing state bills that would make it harder for pharmacists to switch patients to generic epilepsy pills.
- **The Background:** The foundation says switches may be risky. The FDA says it sees little evidence of that.
- **What's at Stake:** Revenue for drug makers. Several popular pills will soon face generic competition.

Four major brand-name drugs used for epilepsy are expected to lose patent protection and face generic competition between next year and 2010. Those four drugs generated $5 billion in U.S. sales last year, according to IMS Health, meaning the state legislation could have a significant bottom-line impact. Some of the $5 billion figure reflects sales of the drugs for other ailments.

Generic drugs are the centerpiece of efforts to tame growth in America's prescription-drug bill, which topped $270 billion in 2006. When a doctor writes a prescription for a brand-name drug, pharmacists are usually permitted in most states to make an automatic switch to a generic judged equivalent by the FDA.

The epilepsy legislation would carve out an exception to that rule, with many of the bills requiring that doctors explicitly approve such a switch. Tennessee has passed a weaker version that requires doctor notification but not consent. Around 25 other states have considered some form of restriction in the past year.

ON THE TABLE

Model legislation the national Epilepsy

It isn't the only health issue where states have been the central battleground. Earlier this year, **Merck** & Co. drew fire for lobbying states to require that preteen

Foundation has provided to state affiliates to address concerns about epilepsy-drug substitution:

A pharmacist may not interchange an anti-epileptic drug or formulation of an anti-epileptic drug, brand or generic, for the treatment of seizures (epilepsy) without prior notification of and the signed informed consent of such interchange from the prescribing physician and patient, or patient's parent, legal guardian or spouse of such person.

Source: Epilepsy Foundation

girls receive its cervical-cancer vaccine to attend school. Merck stopped its direct lobbying in February, but a group of female state legislators that has received funding from the drug maker continue to push for the laws.

States often move faster than Congress, says Jan Faiks, who runs state policy for the Pharmaceutical Research and Manufacturers of America, or PhRMA, the drug industry's trade group. State legislation can move "from idea, to passage, to governor's signature in 90 days, sometimes faster than that," she says. "So the action is in the states."

Campaign contributions to state candidates by pharmaceutical manufacturers and their employees rose to about $8.8 million for 2006 from about $4.6 million for 2000, according to the National Institute on Money in State Politics. Drug makers spent more than $44 million on state lobbying in 2003 and 2004, the last years for which figures are available, according to the Center for Public Integrity.

In state legislatures, as in Congress, the drug industry often enlists nonprofit health and patient-advocacy groups to advance its agenda. In the epilepsy case, the Epilepsy Foundation's state affiliates, rather than the companies, are taking the most prominent part in the lobbying.

The foundation and its state affiliates receive funding from the epilepsy-drug makers. **GlaxoSmithKline** PLC and UCB SA donated $500,000 to $999,999 each in fiscal 2006 to the national foundation, according to its annual report. **Abbott Laboratories** and a **Johnson & Johnson** unit each contributed $100,000 to $499,999. Representatives of four drug companies sit on the foundation's board, as does PhRMA chief Billy Tauzin.

Top Treatments

U.S. sales of prescription drugs used to treat seizure disorders, in millions:

	2007 (Jan. to April)	2006
Topamax	$656.6	$1,825.4
Lamictal	638.9	1,684.3
Lyrica	306.8	727.8
Keppra	299.7	710.5
Depakote	257.1	770.4

Note: Sales figures include prescriptions for other uses such as migraine prevention (Topamax and Depakote), bipolar disorder (Lamictal and Depakote) and neuropathic pain (Lyrica)

Source: IMS Health

The foundation and its affiliates had about $77 million in revenue in 2005, about $48 million of which came from state and federal grants.

The foundation says its diverse funding base shields it from undue drug-company influence, and the industry executives on its board didn't participate in discussions of the drug-switching issue. Foundation leaders note that the state bills would generally require doctor permission for several kinds of switches, including when a patient goes from a generic to a brand.

"These are people's lives that we're talking about -- nothing about stock options and stock value and how this would affect [companies'] bottom line. That would be insulting to us to have discussions like that," says Sindi Rosales, the head of a foundation affiliate in Texas, one of the states that weighed legislation this year. She says pharmaceutical companies are "fabulous partners" and their help in several areas "has been amazingly tremendous," but the companies leave it to the foundation to call the shots.

For their part, company executives describe their lobbying role as limited and say the bills were primarily an initiative of the foundation, although they acknowledge in certain cases that company officials have gotten directly involved. Executives say the aim of these activities is to protect the health of patients. "Our issue is not selfish toward our individual product," says Richard Denness, a vice president at Belgium-based UCB. "It's a real concern in the minds of prescribers.... All it takes in the scheme of things are one or two patients to have a tragic event."

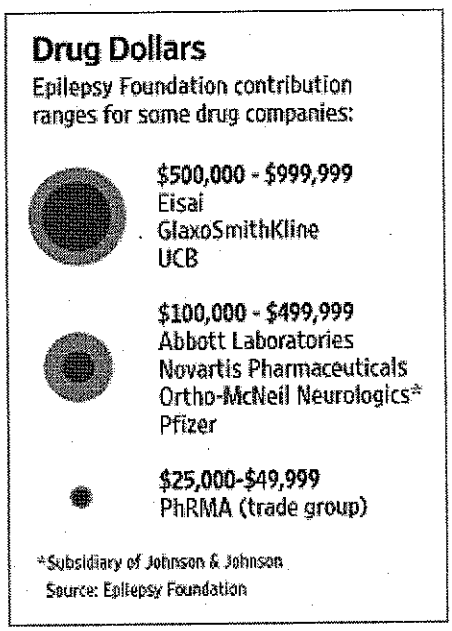
In the late 1990s, the national Epilepsy Foundation, based in Landover, Md., raised concerns about anecdotal reports that some patients experienced seizures and side effects after switching epilepsy drugs. Some of the episodes involved patients who had been switched to a generic from a branded drug. The foundation also worried about cases in which patients were switched from one generic version of a drug to another generic version of the same drug.

When the FDA approves generics, it requires manufacturers to show in human studies that their copycat pills deliver a similar amount of active ingredient to the bloodstream as the brand-name original. However, the agency doesn't require exact equivalence. That would be an impossible bar to clear, because there is always a slight variation in the way people absorb drugs.

The foundation theorized that some generic pills had a meaningful difference from the brands. This difference, it postulated, meant patients were getting more or less of the drug in their blood, causing some of them to have seizures or side effects. Foundation officials floated the idea in a 1999 meeting with the FDA.

The FDA's response: "Show us the data," recalls Sandy Finucane, who oversees state and federal policy for the foundation. The agency, unpersuaded by what it saw, stood firm in its long-held position that the difference was too small to have a tangible impact on patients.

Coming up with the kind of evidence the FDA sought would have required a major clinical trial to demonstrate that the seizures were a direct result of the switches, Ms. Finucane says. The foundation thought it would be difficult to enroll patients for such a trial, and the costs were prohibitive, she says. For years the foundation didn't push the matter, beyond developing policy statements and encouraging patients and doctors to report problems to the FDA.



In early 2006, the issue re-emerged as legislation requiring doctor permission for switches was proposed in Illinois. That's the home state of Abbott Laboratories, which makes Depakote, a leading epilepsy pill that is expected to face generic competition next year. The bill passed, but in watered-down form. An Epilepsy Foundation official in Illinois says Abbott helped fund lobbying for stronger provisions that were considered this year but didn't pass. Abbott said it supports some foundation initiatives but declined to give specifics.

In May 2006, the national Epilepsy Foundation convened a committee of medical experts to examine the question. The committee found a lack of authoritative studies showing that such drug switches cause problems, says its chairman, Steven Schachter, a Harvard Medical School

neurologist. Nonetheless, it recommended that doctors give explicit approval for switches, citing anecdotal reports of seizures and noting that such attacks can be serious.

Last fall, the American Academy of Neurology issued a statement making a similar recommendation. The academy says it receives funding from drug makers for educational programs but not for developing medical guidelines.

At a meeting last September, the national foundation told its local affiliates that if they wanted to push for legislation regulating switches, the foundation would provide model legislation and support, Ms. Finucane says. It also told them to "maintain independence from any company that's going to be interested in this issue," she adds. The 50-plus affiliates operate largely autonomously.

The sponsor of a bill in Georgia, state Rep. Charlice Byrd, says a UCB official was the first person to raise the epilepsy-drug switching issue with her. The Belgian company makes the epilepsy drug Keppra. Ms. Byrd says she was sympathetic because her late mother had epilepsy.

Charlotte Thompson, who joined the foundation's Georgia affiliate as executive director last September, says she became aware of the bill after hearing about it from UCB. "When we realized [Rep. Byrd] was introducing this and looked at it and studied what it was, then we jumped on the bandwagon," Ms. Thompson says. Six lobbyists for three companies joined a committee created by the Epilepsy Foundation to work on the legislative process, she says.

Ms. Byrd says several pharmaceutical-company lobbyists offered their support. Abbott lobbyist Guy Mosier "was extremely helpful working with legislators to help them understand the importance and that this piece of legislation was strictly for patient protection," Ms. Byrd says. Mr. Mosier declined to comment.

Ms. Byrd introduced the bill in the Georgia House in January of this year. At a Feb. 7 hearing of the House's health committee, Lasa Joiner, executive director of the Georgia Psychiatric Physicians Association, testified in support. Ms. Joiner was at the time also a Glaxo lobbyist, which she didn't mention at the hearing. In an interview, she said she didn't raise her tie to Glaxo because the company hadn't asked her to lobby for the bill.

Two days later, epilepsy patients and parents of patients visited lawmakers' offices to ask them to support the bill. The Epilepsy Foundation's Ms. Thompson says drug-company lobbyists accompanied the visitors.

Kimberly Oviedo says her 6-year-old daughter had seizures last year after being switched to a generic version of the epilepsy drug Zonegran. She says she supported the bill because she wouldn't "want any other person to have to go through what we've been through with our kids." Ms. Oviedo also has a son who suffers from epilepsy.

The bill passed the Georgia House in a 161-0 vote on Feb. 28, but it stalled in the Senate after groups representing pharmacists and generic-drug makers mounted heftier opposition to it in that chamber. Pharmacies often earn bigger profit margins on generics than on branded drugs.

Ms. Thompson says the foundation plans to meet with the Georgia Senate leadership this summer to try to gather its support for next year.

In Texas, two local Epilepsy Foundation affiliates decided to approach an Abbott official after

they resolved to push for a bill, says Ms. Rosales, the head of one of the affiliates. Abbott and other drug makers helped fund the foundation's Texas lobbying, she says.

Ms. Rosales, whose daughter used to have seizures, says she felt deeply about the bill but worried about being perceived as a "mouthpiece for the pharmaceutical industry." She nonetheless hired Santos Alliances, a firm that also represents PhRMA, as her affiliate's lobbyist. Ms. Rosales says it's difficult to find a health-care lobbyist with no drug-maker clients. Frank Santos, head of the lobbying firm, says PhRMA was "absolutely 100% not involved" with the bill.

At a March hearing in the Texas Senate, Ron Hartmann, a lobbyist for a generic-drug maker owned by Novartis AG of Switzerland, testified against the bill. He said he suspected the bill was "less focused on the citizens of Texas than on protecting the market share of a few brand-name drugs that are scheduled to go off-patent in the next few years."

State Sen. Kyle Janek, the bill's sponsor, responded that Mr. Hartmann had "impugned my motivations," and added that, if Mr. Hartmann would "abstain from doing that," then he would abstain from calling Mr. Hartmann a "high-priced shill." Mr. Hartmann apologized. In 2006, Sen. Janek received about $19,000 in campaign contributions from drug makers. He says he sponsored the bill because it was in the best interests of patients.

The bill passed the state Senate in April, but failed to come up to a vote in the House after debate in that chamber's health committee. Three of the committee's members said in interviews later that they were skeptical of the bill because they thought it was being pushed by drug companies. Generic-drug makers and pharmacists lobbied heavily against the bill.

Meanwhile, some doctors are pushing harder for a study that would settle the matter. Michel Berg, a neurologist who is chairman of an American Epilepsy Society task force examining the switching issue, has opened discussions with the FDA about what kind of trial would be necessary.

For now, Gary Buehler, the director of the FDA's office of generic drugs, says the agency is skeptical that the drug switches cause seizures. "The only way you can somehow pin this down is to do a good study," says Mr. Buehler.

Write to Sarah Rubenstein at sarah.rubenstein@wsj.com[1]

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Testimony from the Pharmacy Society of Wisconsin
Before the Assembly Committee on Public Health

Senate Bill 71

Tom Engels, Vice President of Public Affairs

Wednesday, January 30, 2008

PHARMACY SOCIETY OF WISCONSIN

"Leading Our Profession in a Changing Health Care Environment"

The Pharmacy Society of Wisconsin opposes the passage of Senate Bill 71 because this legislation will not offer the protections to people with epilepsy that are implied by the bill. Pharmacists fully respect the right of people with epilepsy to obtain medications that offers them the best treatment. That exists today.

But the reality is, their treatment is not solely up to them. It is not up to pharmacists, it is not up to their physicians, it is up to the pharmacy benefit manager that is responsible for managing the prescription drug claims for their health insurer.

This legislation is similar to legislation that has been introduced in approximately 16 other states and has been financially supported by pharmaceutical manufacturers.

This legislation has been introduced at the request of the Epilepsy Foundation that would prohibit the substitution of prescription medications used for the treatment of epilepsy. This legislation is similar, but not identical, to a proposal that was introduced in the last Wisconsin legislative session. To date, no state has enacted this type of policy.

Under the provisions of this bill, a pharmacist would be prohibited from substituting an equivalent generic medication for its brand counterpart and from substituting a generic medication from one manufacturer for an equivalent generic medication made by another manufacturer, for all prescription products used in the treatment of epilepsy. A substitution would only be allowed with the consent and authorization of both the prescribing practitioner and the patient (or the patient's spouse, parent or legal guardian). Patients who have been diagnosed with epilepsy should have their condition carefully monitored and they should not have their treatment options inappropriately limited by insurance company policies.

Generic Substitution in Wisconsin

As it relates to interchange of prescription drug products, Wisconsin has taken a common and conservative approach that relies upon a sophisticated therapeutic equivalency testing process of the Food and Drug Administration (FDA). In Wisconsin, medications available for substitution only include those that meet the most rigorous equivalency tests and that receive the FDA's A/B rating.

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Wisconsin pharmacists work everyday to help patients in their medical treatments and help to reduce the cost of prescription medications by dispensing lower cost generic medications. In fact, Wisconsin law requires pharmacies to dispense a therapeutically equivalent generic prescription drug if it is lower in cost. This practice has been proven to help lower the cost of health care while maintaining the quality of treatment.
There are some instances where a prescribing practitioner will request that a specific medication be dispensed to a patient. In that case the prescribing practitioners will indicate that directive by writing "dispense as written" (DAW) on the prescription order. Most insurers and health plans provide a system for such a product to be considered for approval, dispensing and reimbursement.

Related Information
In the co-sponsorship memo that was circulated to legislators there was a reference to injured Iraq war military personnel who suffered severe head injuries. Ironically, active duty military personnel can receive any prescription drug they are prescribed — the United States Department of Defense (DoD) doesn't have a prescription drug formulary (a selected list of drugs that can be dispensed). However, when a member of the armed services leaves active status he or she becomes eligible for medical care, including prescription drugs, from the Veterans Administration (VA). Although the VA pharmacy system does employ a prescription drug formulary, VA pharmacies are not subject to Wisconsin pharmacy laws and regulations, including the provisions of this bill, should it become law.

Unintended Consequences
Some medications are prescribed for multiple symptoms, including epilepsy. The legislation would prohibit substitution of these medications if they are used in the treatment of epilepsy, but not if they are used for other conditions.

Patients receiving a generic epilepsy medication may find it difficult to receive treatment when the pharmacy provider selects an alternate generic manufacturer of the epilepsy product. It is common for a pharmacy or the pharmacy's wholesale distributor to change sources of generic products based upon the availability of the product and pricing advantages from one manufacturer over another. Changes in generic supply can change literally every month. It is possible that a patient would be unable to locate a pharmacy that stocks the very same generic manufacturer's product. Patients would also be set-up for failure as they are admitted or discharged from a hospital that may stock a different generic manufactured product than what the patient had received from a community pharmacy. Further, generic medications cost about ¼ of the brand-name medication cost, on average, although the difference varies from medication to medication. If enacted, this legislation will result in higher health care costs — for epilepsy patients, businesses and insurers alike.

Proponents Raise Concerns with the Bioequivalence of Substituted Products
The major concerns raised by proponents of this legislation are problems that may arise with the substitution of any medication used in the treatment of epilepsy. They argue that patients who have epilepsy should be allowed to maintain access to the same medication by the same manufacturer in order to minimize the potential of a seizure due to therapeutic differences between products. To illustrate this point, advocates reference the bioequivalence of generic medications not only from their brand name counter-parts but also from generic to generic.

The United States Food and Drug Administration states, "a generic drug is the same as a brand name drug in dosage, safety, strength, how it is taken, quality, performance and intended use. The FDA bases evaluations of substitutability or "therapeutic equivalence" of generic drugs by requiring and testing that the drug product contains identical amounts of the same active ingredient(s) as the brand name product. Drug products evaluated as "therapeutically equivalent" can be expected to have equal effect and no difference when substituted for the brand name product."

Bioequivalence of different versions of a drug can vary by up to 20% (80-120%), because for most drugs, such variation does not noticeably alter effectiveness or safety. However, actual differences between FDA-approved generic and trade-name drugs are generally much smaller than the allowable 20%. The FDA reports that actual differences are 3.5% on average and rarely exceed 10% in any single study of bioequivalence.

PSW recognizes that sometimes generic substitution is not appropriate. For example, some generic versions cannot be determined to be bioequivalent to the original drug because no standards for comparison have been established. These versions should not, and in Wisconsin may not, be interchanged for the original drug.

PSW Recommended Action
While the intent of the proponents of this legislation is understandable, the negative consequences associated with its passage are clear. PSW recommends that the legislation be rejected. PSW further recommends that the Office of the Insurance Commissioner ensure that patients with epilepsy are not inappropriately denied access to necessary therapies by their insurer or health plan.

Warren La Duke
210 S. Academy St
Stoughton, WI 53589

I am here to share my experience with generic medications that were substituted to me through my regular prescription for seizure control without my knowledge or consent.

In January 2006, while taking Keppra and Zonigran my seizures were well controlled. Beginning with my February monthly refills, and continuing for four months, the Zonigran prescription was substituted with a generic version unbeknown to me. Within a week of taking these generic prescription there was a noticeable change in my seizure activities.

Ultimately this change resulted in my having complex partial seizures again, and I had to voluntarily hand in my driver's license until my seizures were once again under control. As a result of appointments with my neurologist and an understanding pharmacist willing to work with me I was able to get back on the medication that was prescribed and get my seizures under control once again.

I consider myself one of the lucky ones because of the excellent health benefits provided to me through my work. I'm able to get some extra time off to make the necessary appointments to see my doctor when the time is available, to get the brand name medications, and find ways to get around the temporary limitations created when I lose my drivers license.

Unfortunately, many people who have epilepsy as a pre-existing condition often struggle with their health coverage and are not provided the cooperation from their work. Because of cost, or their health coverage, they end up taking the generic brands. When pharmacies switch the generic brands from manufactures so often, as they did with myself, problems similar to mine will continue and a person may never get their seizures under control just because of the constant change. It's almost like taking a new medication with every switch in manufacture brand.

Therapy failure for epilepsy means either a breakthrough seizure if your blood level gets low or toxicity if it goes too high. With generics the difference is enough to make such a difference. By informing both the patient and the prescribing physician, we can help avoid any unnecessary therapy failure, unnecessary expense and difficulty maintaining health at work or school.

dister. by Express Scripts

ANTICONVULSANTS

NONSPECIALTY RANK 7

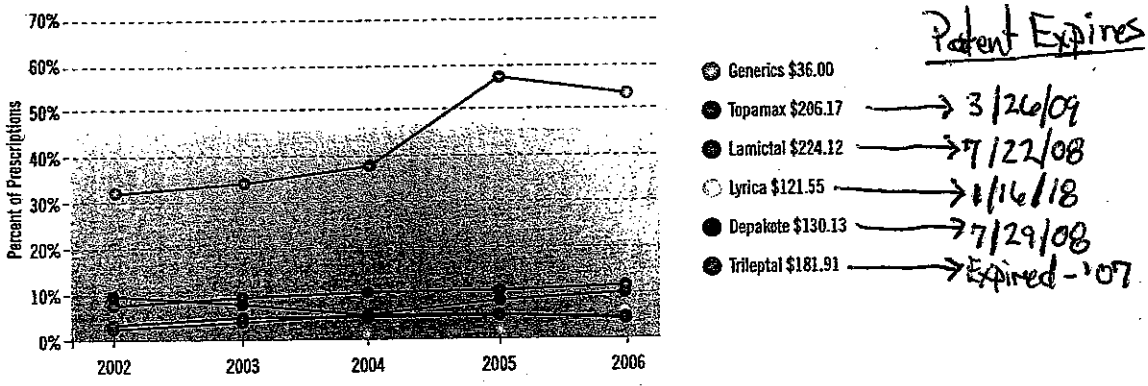
COMPONENTS OF TREND 2005 TO 2006

Cost per Prescription		**5.5%**
Price	0.6%	
Units per Prescription	-0.3%	
Brand/Generic Mix	-1.6%	
Therapeutic Mix	6.9%	
Utilization		**7.9%**
Prevalence	9.2%	
Intensity	-1.2%	
New Drugs		**0**
TOTAL		**13.8%**

KEY FACTS 2006

Cost PMPY: $24.60
 # Rx PMPY: 0.25
Prevalence of Use: 3.4%
Average Cost/Rx: $97.80
 # Rx/User/Year: 7.31

Anticonvulsants Market-Share Trend



Patent Expires
Topamax → 3/26/09
Lamictal → 7/22/08
Lyrica → 1/16/18
Depakote → 7/29/08
Trileptal → Expired - '07

- Trend in this category increased from 3.4% in 2005 to 13.8% in 2006. While utilization trend for anticonvulsants is not much higher than the previous year's trend, the cost component rebounded in 2006 as the impact of generics to gabapentin declined.
- Utilization of Lyrica® increased in 2006, mostly due to a new FDA-approved indication for the treatment of nerve pain associated with diabetes.
- Off-label use continues to expand this market because anticonvulsants are often used for conditions such as bipolar disorder, neuropathic pain and migraine prophylaxis.

Drug	Indication	Pipeline or Patent Expiration	Anticipated Availability
Xilep® (rufinamide)	Epilepsy	Pipeline	2008
Trileptal® (oxcarbazepine)	Epilepsy	Patent Expiration	2007
Depakote®/Depakote ER (divalproex/divalproex extended release)	Epilepsy/ Migraine	Patent Expiration	07/29/2008*

**Litigation*

Epilepsy Foundation of Western Wisconsin
Kristin Berg
4903 Jeffers Rd. Eau Claire, WI 54703
Lou Kelsey
715 E. Tyler Ave. Eau Claire, WI 54701
Assembly Hearing Testimony for ~~AB150~~ SB 71
January 30, 2008

Case Study #1:
Josh was a male High School student who was very shy and hadn't had any seizures for a 2 year period of time. He was just starting to come out of his shell and socialize with other kids his age when he first had trouble with his medication. When he picked up his meds at the pharmacy he noticed that they looked different but was told that it wasn't a problem – they were just a generic form of his prescribed medication. Within 3 days Josh began having break through seizures to the extent that he had to be hospitalized. His physician put Josh through extensive testing to find out the cause of the seizures because he was not aware of the medication switch by the pharmacy. Josh fell behind in school because of all of the days he had to miss and he had to delay beginning drivers education classes until he was seizure free for the required 90 day period. Through further testing, it has been discovered that Josh must be on the brand name medication to ensure proper seizure control. His parent's insurance will only cover the generic form of Josh's medication, so his parents must pay the full price of his medications out of pocket, which is putting a significant strain on their finances.

Case Study #2:
Joe is a 52 year old single male who receives Governmental Assistance because of his epilepsy. He recently had his medications switched to a generic and has had considerable negative side effects. Joe has had to reduce his work hours because of a lack of stamina. He is also extremely tired all of the time and has sleep and emotional problems. Because Joe is on a limited income, he cannot afford to pay for the brand name of his medication, even though he knows it would improve his whole situation. Governmental Assistance will only pay for the generic form of Joe's medication, so that is what he continues to take, despite all of the side effects.

Case Study #3:
Kristi is a mother of two who has had epilepsy for over 10 years. She picked up her medication, which had been switched to a generic form, and within days began having increased seizure activity and unpredictable mood swings. Family members who were gravely concerned about the change in her behavior contacted the Epilepsy Foundation for help. At her family's urging, Kristi contacted her physician. She was put through a complete series of tests, including blood levels, and it was determined that the level of medication in her blood stream was very low. Kristi's physician stated that she must stay on the brand name of her medication in order to keep her blood levels in an acceptable range. It was only after Kristi had many terrible seizures and mood swings and went through a full battery of medical tests that her insurance company would cover the cost of the brand name medication.